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Clinical Reviews in Andrologic Endocrinology:

[Testicular Dysfunction]

I. Physiology, Functional Pathology and Diagnosis

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THERAPY OF deficient testicular function is indicated chiefly for two reasons, *a*), the rational treatment of various hypogonadal states in which alterations of body habitus assume clinical importance, and *b*), the correction of seminal inadequacy which impairs fertility. The internist, urologist and endocrinologist usually originate and supervise the therapeutic approach to the former group; the gynecologist, as a part of the gynecologic and andrologic investigation of barren couples, usually initiates investigation of the fertility of husbands.

Professional contact is established when the wife of one of these couples seeks the gynecologist's advice as to why she has not become pregnant. Since, as a rule, the husband has not considered the likelihood of his sexual function being at fault, the responsibility of orienting him as to the necessity for, and the scope of his examination usually falls upon the gynecologist. Frequently, the seminal studies must be made by the gynecologist or his trained assistants rather than relying upon the urologist for these data; this fact often closely associates the gynecologist with the results of any therapeutic endeavors which may be necessary in the husband's case. His counsel is sought by the husband and by the wife as to the prognosis, when all of the diagnostic data have been collected. Good sound clinical judgment of the gynecologist may prevent unwarranted therapeutic exploitation of husbands by overly endocrine-conscious consultants.

In the fertility group, symptoms and signs commonly ascribed to hypogonadism are often lacking, although it is to be recalled that seminal inadequacy, either relative or absolute, is manifested in both groups of patients. For orientation, therefore, review of seminal and endocrine physiology of the testes, endocrine pathology and the diagnosis of gonadal levels of function is pertinent.

ENDOCRINE PHYSIOLOGY

The physiologic rôle of the testes is a two-fold one, *a*), to produce an abundance of healthy spermatozoa for the fertilization of ova, and *b*), to supply a hormone, testosterone, capable of producing growth, differentiation and functional adequacy of normal adult sexual apparatus.

Spermatozoa develop from the spermatogonia of the seminiferous tubules. Testosterone is thought to be

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secreted by the Leydig cells in the interstices of the testis. Both the seminal epithelium and the interstitial elements, i.e., the exocrine and the endocrine functions, are dependent for normal activity upon the gonadotropic influences of the anterior lobe of the pituitary. It has been assumed generally that the gonadotropic complex which is responsible for luteinizing phenomena in the female is concerned with tropic influences upon the interstitial elements of the testis while that complex which governs follicle maturation in the female produces stimulation of the germinal epithelium of the male.

These gonadal-pituitary interrelationships have been established from experimental data secured by studies upon laboratory animals. Some generalizations from these data are: *a*), Removal of the pituitary produces testicular atrophy which involves both interstitial and germinal elements. *b*), Castration results in hyperactivity of gonadotropic function of the pituitary, associated in some species with characteristic cytologic alterations of the gland. *c*), Implants of pituitary glands or injections of active gonadotropic extracts repair post-hypophysectomy damage, if this has not proceeded too far or existed too long. *d*), Implants of testis or injections of active androgenic extracts (or crystalline testosterone or its esters) restore normal pituitary function after gonadectomy.

Van Dyke (1), however, has summarized data which conflict with the generally accepted concept of biphasic specificity of the pituitary gonadotropic complexes. *a*), Either factor of the gonadotropic complex will support spermatogenesis in mature hypophysectomized male rats but the luteinizing fraction is necessary for maintenance of the interstitial cells. *b*), In the same test animal, spermatogenesis can be maintained if androgens are given promptly after hypophysectomy. *c*), The pituitary of the intact male rat apparently secretes only the follicle-stimulating fractions, although small amounts of the luteinizing fraction have been encountered after implantation of pituitary tissue in this animal.

Increases in the gonadotropic activity of the pituitary produce increased testicular activity which results in the outpouring of additional testosterone, the effect of which is to depress pituitary function. On this basis the existence of another hormone, thought to be produced by the germinal epithelium and to be concerned with the regulation of the tropic effects of the pituitary upon this epithelium, has been suggested by some investigators. Despite some supportive evidence from clinical and laboratory data factual proof that the testis secretes a second hormone has not been advanced.

Clinical observations support these concepts of gonadal-pituitary interrelationships. Gonadal failure, both exocrine and endocrine, is common in pituitary disease, i.e., adiposogenitalism, pituitary dwarfism, pituitary cachexia and basophilism. The grades of hypogonadism which are associated with various alterations in pituitary function have not been defined as clearly as desirable, in regard to either germinal or endocrine levels of function. The clinical findings in severe grades of pituitary failure, however, are striking and unequivocal.

Thyro-gonadal interrelations have been delineated even less clearly. The good therapeutic results which follow the 'empiric' use of thyroid substance in patients of both sexes with lowered fertility support the belief that close integration of the functions of the thyroid and gonads exist. On the contrary, hypometabolism may exist in individuals of either sex with little demonstrable evidence of endocrine or germinal impairment (2).

Experimental data from laboratory animals indicate that, as a rule, disturbances in thyroid function impair spermatogenesis. Some animals, as Moore (3) has observed, appear to be singularly independent of the thyroid in this regard, i.e., the frog tadpole (Allen, 1918, quoted by Moore) and the immature rat (Ross, 1936–1938, quoted by Moore). Moore has concluded from a review of the experimental data that no direct relationship has been established between the thyroid and the testis and that good evidence exists that the indirect associations are mediated by way of the alterations in metabolism.

While pertinent interrelationships of the thymus and pineal with testicular function have been suggested, only the pituitary has been proven to have a dominant rôle in the sexual physiology of the male. Normal sexual function requires an adequate level of general health so that diseases or functional alterations in any of the glands, as well as chronic or acute constitutional diseases, inanition, avitaminosis and intoxications induce alterations in testicular function; these, however, are, for the most part, indirect rather than direct influences upon the endocrine system.

ENDOCRINE PATHOLOGY

Alterations in testicular function may arise from diverse causes; failure may result from intrinsic inadequacy of the gonads or from damage produced by disease or trauma; it may be secondary to disturbances in other endocrine glands or it may be due to secondary depressing effects of constitutional disease or impairment. These various etiologic factors produce fluctuations in the gonado-pituitary reciprocities, important elements of which are levels of hormonal secretion and receptivity or responsiveness of end organs.

Gonadal failure may be of two types; it may embrace both the endocrine (interstitial) and exocrine

(seminal) functions; or it may be characterized by seminal failure alone. No clear-cut instances of endocrine failure with persistence of normal germinal activity exist. A suggested classification for gonadal failure is the following one.

I. Androgenic and seminal failure (hypogonadism)
  1. Intrinsic or primary in gonads
    a. Adolescent hypogonadism due to embryologic faults or disease
    b. Senile hypogonadism
    c. Hypogonadism due to acquired disease (orchitis) or tumors
    d. Surgical or roentgenologic hypogonadism
  2. Hypogonadism, secondary to other disorders
    a. Due to pituitary disease
    b. Due to diabetes mellitus
    c. Due to adrenal disease
    d. Due to causes primarily extra-endocrine in nature

II. Seminal failure, without androgenic failure
  1. Intrinsic in gonads due to failure of descent
  2. Due to thyroid disease
  3. Due to adrenal disease
  4. Extra-endocrine, due to toxins, chemicals, high fever and sexual excess

The various alterations in endocrine levels and in end-organ responsiveness which characterize these various types of testicular failure are reviewed briefly.

Intrinsic hypogonadism. No significant impairment of pituitary function occurs. Due to the absence of the 'conditioning' action of normal androgenic levels, a compensatory hypergonadotropic state in the pituitary may ensue, designed to overcome the characteristic relative non-responsiveness or refractory state of the gonads.

A brief consideration of the basic pathology under these circumstances affords little rationale for gonadotropic therapy. Various grades of hypoplasia or aplasia result from embryologic faults or fetal diseases, such as syphilis. Gonads are rarely absent. Hypoplasia involves both germinal and interstitial elements. Small fibrous nodules in the scrotum may constitute the only vestige of gonads.

It is correct to assume, perhaps, that senescent hypogonadism of the male, as in the female, is due to development of an intrinsic refractivity of the gonads, although, as Engle has observed (4), the degenerative changes in the testes are not as striking as those in the ovaries. The increased excretion of gonadotropins in aging man is not as definite as that in the climacteric woman. Despite thickening of the basement membrane of the seminiferous tubules and of the surrounding tunica propria which is probably the results of altered vascularity, evidences of active spermatogenesis have been observed in the testes of men in the sixth and seventh decades of life. The integrity of the physiologic functions of the seminiferous tubules is accepted generally as evidence of adequate endocrine function of the gonads. While it has been said that the interstitial function outlasts the seminiferous one, the most striking changes of the sexual apparatus in aging occur in the prostate.

Local diseases of the epididymis or the funicular structures, and certain surgical procedures which interfere with testicular circulation, may result in various degrees of testicular fibrosis and atrophy with consequent functional impairment. Orchitis, complicating many diseases, may be followed by varying aberrations. These alterations which are often focal rather than general and involve both the interstitial and germinal elements, include impairment of vascularity, fibrosis and focal necrosis, and hyalinization of the seminiferous tubules. In advanced grades of testicular atrophy, the seminiferous epithelium may be reduced to a state of rather complete degeneration in which only a few Sertoli cells remain. While various drugs and chemicals exert profound gonadopathic influences, these affect, for the most part, the germinal rather than the interstitial elements and are discussed, accordingly, in the consideration of seminal failure occurring without significant endocrine impairment. The functional break in this group of conditions occurs in the end-organ or gonad portion of the pituitary-gonad axis with the result that any alterations which may occur in pituitary levels of function are in the order of increases rather than decreases.

Testicular tumors tend to produce seminal and usually androgenic failure. These tumors include those originating in *a*), connective tissue, fibromata and myomata, or *b*), seminiferous epithelium, seminomata, and they have no intrinsic endocrine secretion; those originating from *c*), misplaced or embryonal sex cells, teratomata, chorion-epitheliomata, or from *d*), interstitial tissue, such as adenomata of undescended or atrophic testes, neoplastic-like hyperplasia; these are associated frequently with alterations in endocrine function, such as an increased secretion of gonadotropins, androgens or estrogens. Despite the increased androgenic secretion of some interstitial cell tumors, which may result in precocious adolescence, damage to the seminiferous elements may occur as the result of depression of pituitary function induced by the high androgenic titers. Chorion-epitheliomata, causing at times gynecomastia and lactation, may produce atrophy of the uninvolved testis due to the direct action of the large amounts of estrogenic secretion and to pituitary depression. Unilateral testicular tumors of non-endocrine nature may cause little apparent endocrine or seminal impairment, if the uninvolved testis is healthy and capable of compensation.

Similar observations characterize the endocrine and germinal pathology which follows roentgenologic damage to the gonads. The early effects of testicular irradiation are on the spermatogenic cells, involving the least differentiated elements, the spermatogonia, and progressing, when severe damage has been inflicted, to a complete destruction of the germinal epithelium except, perhaps, for a few Sertoli cells. When there has been heavy irradiation, the interstitial elements are destroyed and fibrous atrophy of the testes ensues.

Hypogonadism, due to pituitary disease. Clinical syndromes resulting from pituitary disease are characterized generally by hypogonadism. No initial intrinsic aberrations occur in the gonads as regards their responsiveness, although, as Van Dyke (1) has observed, some experimental studies indicate that even a short period of pituitary deficiency may lessen markedly their sensitivity to therapy. Under these circumstances, it would seem likely that promptly initiated and adequately administered gonadotropic therapy might be able to restore normal gonadal function.

Hypogonadism may characterize some syndromes in which hyperactivity of certain functions of the pituitary exist, i.e., acromegaly and giantism. Several explanations have been suggested for this. Gonadotropic function of the pituitary may be suppressed by the increase in other functions, i.e., growth; the gonads may be overstimulated with subsequent atrophy; the gonadotropic function of the pituitary, in turn, may be depressed by the increased outpouring of androgens.

Pituitary-gonadal reciprocities have been defined clearly from studies upon the effects of hypophysectomies of various experimental animals, as the result of the pioneer work of P. E. Smith. The effects of pituitary failure on the gonads and accessory sexual apparatus are illustrated best by the characteristic findings in hypophysectomized monkeys (5). In the testes of the adult hypophysectomized monkey only an occasional spermatogonium remains on the basement membrane. Indifferent or Sertoli-like cells make up the bulk of the seminiferous epithelium. The appearance becomes characteristic of that of prepubescence in the monkey and in the human male. Although the Leydig cells become functionally inactive, few striking cytologic alterations occur. Atrophic changes in the accessory sexual apparatus occur, however; these are of the same order as those which follow castration. From this description, it is evident that hypophysectomy or pituitary failure induces both germinal and endocrine failure of the testes.

Of the various pituitary syndromes, that of pituitary cachexia (Simmonds' disease) yields the most striking degree of gonadal failure, one which is comparable to that observed following hypophysectomy. The other syndromes, such as pituitary dwarfism, adiposogenitalism, acromegaly and pituitary basophilism as well as those instances in which neoplasms about the pituitary interfere with its function, are characterized by various grades of gonadal failure, which involve both endocrine and germinal elements.

Hypogonadism, due to diabetes mellitus. Decreases in sexual potency, progressing at times to complete impotency and lowered fertility occur commonly in severe diabetics. Since these symptoms of hypogonadism are not always corrected by adequate dietetic measures and insulin therapy, they cannot be related in their entirety to the effects of the disturbed metabolism, malnutrition and cachexia produced by the disease. In the chronic cases, Koch (6) regards the cause of testicular impairment as circulatory in origin, due to the development of arteriosclerosis.

There is a surprising paucity of descriptions of sexual alterations in this condition. Warren (7) has observed no testicular alterations other than cessation of spermatogenesis and some increase in the thickness of the basement membrane of the tubules. He states that in the adequately treated patient there is no alteration from the usual testicular picture. Koch (6), however, has observed atrophy of the seminiferous tubules, followed in some instances by increase in interstitial tissue. Kyrle (8) describes the occurrence of testicular atrophy of the same order as seen in conjunction with severe metabolic disease, acute and chronic infections and diseases of the circulatory system. The fact that, under adequate therapy, normal gonadal function returns in many instances indicates the likely existence, prior to therapy, of a disturbed pituitary function secondary to metabolic and nutritional factors and the possible non-existence of any significant aberration in gonadal responsiveness. In the instance wherein hypogonadism continues despite adequate diabetic therapy, it seems reasonable to infer that circulatory alterations have produced intrinsic testicular damage of such degree as to render the testes unresponsive to normal pituitary influences.

Hypogonadism due to adrenal disease. In the hypocortical syndrome (Addison's disease), hypogonadism is common. Decreases in libido and lowering of fertility occur. Rowntree and Snell (9) and Grollman (10) describe the association of testicular atrophy with the disease. This involves both the germinal and the interstitial elements. The cause of this hypogonadism appears to be, most likely, a disturbance in pituitary function, secondary to the metabolic disturbances and the cachexia which characterize the disease. That no significant impairment of testicular

responsiveness necessarily follows is indicated by the fact that, during remissions of the disease, or as a result of therapy, adequate gonadal function may return.

Hypogonadism due to causes primarily extra-endocrine in nature. The most common of these are the debilitating effects of acute and chronic diseases, malnutrition and deficiency states. In these conditions, both endocrine and germinal impairment result from secondary alterations in the function of the pituitary. Any direct damage to the testes under these circumstances precludes their normal responsiveness if and when normal pituitary function returns.

As Reynolds and Macomber (11) observed, the testes become soft and decrease in size in malnutrition. Jaffé (12) reported that in chronic diseases the seminiferous tubules were separated by broad and mostly edematous connective tissue. Cordés (13) found spermatogenesis depressed in various acute diseases; he reported that the seminiferous tubules were thickened and the interstitial elements increased in malnutrition. Van Hansemann (14) was of the opinion that some increase in the interstitial cells occurs in all cachexias. Moore (3), however, has observed that these conditions, when severe enough to interfere with pituitary secretion, are always followed by low androgenic secretion. Simmonds (15) has observed that many chronic diseases may produce seminal failure without apparent alterations in the external appearance of the testes. Swelt and K'Ang (16) noted degeneration and hyalinization of the seminal epithelium and Bessey and Wolbrook (17) reported testicular atrophy in vitamin A deficiencies. Testicular atrophy and germinal impairment have been described in vitamin B deficiency; Parkes (18) related these to secondary alterations in the function of the pituitary. The striking effects of vitamin E deficiency in experimental animals, according to Mason (19), involve only the germinal epithelium and are associated with no androgenic deficiency. Jackson (20) has summarized the effects of inanition and malnutrition upon the testes in his general monograph on the subject.

Extreme sexual excesses may lead to hypogonadism. As an example of such excesses, Lepinasse (21) recalls the Mujerados of Mexico, whose sexual decadence was produced by artificial irritation. Consequent to the induced and almost continual spermatorrhea, marked testicular and genital atrophy occurred, associated frequently with loss of pubic hair and gynecomastia. In these instances, it is obvious that the subsequent hypogonadism is caused by direct testicular damage. Alterations, if any, occurring in the pituitary function are in the order of increases. Exhaustion of the testes produces intrinsic refractivity to pituitary influences.

Seminal failure of intrinsic gonadal origin due to failure of descent. The thermo-sensitivity of the seminiferous apparatus of the testes and its dependence for integrity of function upon the efficient scrotal thermo-regulatory function are well known. Ectopia of the testes resulting in inguinal or abdominal locations produces germinal impairment and, if it continues over long periods of time, interference with endocrine function; this may occur in cases classified in *Group I*, also. That these effects are direct testicular ones is obvious. If testicular impairment has not progressed too far, deposition of the testes into the scrotum is followed by a return of germinal and endocrine functions.

Felizet and Branca (quoted by Moore, 3) studied 51 cryptorchid testes. They found that the majority contained no cells of the germinal line. A few showed spermatogonia, but only two contained spermatids. None of the series had produced spermatozoa. Moore (3) has observed that, while the interstitial tissue of the cryptorchid testes secretes androgens, this secretion level may be lower than normal, an opinion which is shared by Korenchevsky (quoted by Moore, 3). Earlier opinions had been stated that often the amount of interstitial tissue was greater than normal and that there was an increase in the secretory activity of these elements. Many experimental data, as well as clinical observations, suggest that there results some endocrine impairment of the testes when the abdominal position is maintained over long periods of time. The studies of Hanes and Hooker (quoted by Moore, 3) upon the androgenic content of scrotal and cryptorchid hog testes bear out this belief.

Seminal failure due to thyroid disease. It is general clinical knowledge that impairment of thyroid function commonly results in disturbances of gonadal function. These thyro-gonadal relationships have been studied more intensively in the female, in whom the gonadal manifestations of thyroid disease are more striking. In neither sex have any thoroughly acceptable experimental or clinical data regarding the *modus operandi* of these effects been accumulated. Salter (22) has suggested three possible types of thyro-gonadal reciprocities; *a*), a 'peripheral sensitization' of tissues by the thyroid principle to gonadal hormones; *b*), effects produced by thyroid principle on the pituitary-gonadal axis, or vice versa; and *c*), indirect effects of the thyroid on the gonads by way of other glands, e.g., the adrenal. Moore (3) considered that thyroid effects upon the gonads were indirect and by virtue of the associated metabolic alterations. Van Dyke (1) has concluded that thyroid

secretion is probably of no great significance in the regulation of gonadal function, its usual effect, if any, being to lessen the action of the follicle-stimulating hormone. The experimental studies of Tyndale and Levin (23) suggested that this is a peripheral effect on the reactivity of the gonadal tissue rather than an effect on pituitary function. The observations of Howell (24) are difficult to reconcile with these views. This worker found increased gonadotropic titers in the urine of patients of both sexes with thyroid diseases, i.e., exophthalmic goiter, myxedema and adenomatous goiter. Our group (2) could find no direct effects of thyroid substance upon the pituitary-gonadal axis.

Meager, indeed, are any exact clinico-pathologic descriptions of the gonads in thyroid disease. General statements abound. Howard (25) observed that genital hypoplasia is not infrequent in hyperthyroidism but that no appreciable anatomic changes occur in the gonads. It may be assumed that the loss of libido and sterility in advanced hyperthyroidism may be due to the effect of the cachexia upon the pituitary function. The sexual-retarding effects of childhood hypothyroidism and cretinism are well known. Howard observed that complete impotence is the rule in cretins and quoted Langhans that the testes and epididymides of a 24-year-old cretin were of 'child-like size' and that spermatozoa were absent or markedly decreased in number. Clinical observations, however, indicate that sterility is not necessarily the rule with moderate or even severe hypothyroidism. Rolleston (26) has cautioned that men with myxedema are not necessarily sterile. Some of the best seminal specimens seen in our clinic were from men with low metabolic rates. Marañon (27) has reported the occurrence of left gynecomastia in two males with hyperthyroidism. There is good reason to believe that the primary gonadal effect of thyroid disease is peripheral and, for the most part, germinal in nature, the disturbed metabolism resulting in the formation of germinally inadequate spermatozoa.

Seminal failure due to adrenal disease. The significant effects of hyperplasia or tumors of the adrenal cortex upon the genital system are well known. The effects are produced by the outpouring of large amounts of androgens. In those cases arising before adolescence, which are those showing the most striking endocrine effects, spermatogenic function of the gonads fails to keep pace with the interstitial function. Germinal inadequacy is common in this condition, its cause probably being related to the depressing effect of the androgens upon pituitary gonadotropins.

Broster et al. (28) reported that their studies of the testes of 13 patients, who had developed adrenal pathology during pre-adolescence, indicated the existence of spermatogenesis in only one case, whereas in 10 cases activity of the interstitial elements was observed. In the group of patients of pre-adolescent age, the testicular histology was not grossly abnormal, except that testicular tubules were less numerous than normal and there was some increase in the stroma. Spermatogenic epithelium appeared quiescent. Those patients of the group, however, who were of post-adolescent age showed a quite different picture. Spermatogenesis was inhibited, with resulting aspermia although the seminal epithelium did not necessarily show atrophy. There was a marked hyperplasia of the interstitial elements, the cells of which often formed large islets between the tubules.

Seminal failure due to extra-endocrine causes. These causes include the action of certain toxins and chemicals, febrile attacks and sexual excess. These effects are essentially local ones on the germinal epithelium without any or with minimal endocrine impairment. Certain toxins and various organic compounds and salts of heavy metals have depressing effects on spermatogenesis itself or on mature spermatozoa. Recently, sulfanilamide has been described as having depressing action on the seminal function (29). Alcohol is said to exert injurious effects on the germinal elements. Tobacco, too, may have harmful effects. Moore (3) has stated that prolonged febrile states are followed not infrequently by temporary sterility. Mills (30) found many instances in which the germinal epithelium was destroyed during attacks of epidemic pneumonia. Experimental studies on the rat (31), guinea pig (32), ram (33) and man (34) have indicated the extreme sensitivity of the spermatogenic apparatus to increased temperatures. On the other hand, spermatozoa are quite tolerant of low temperatures (35). Doubtless, the frequency of intercourse may play a rôle in seminal failure. What may be a normal and physiologic sexual regime for one individual may prove an exhausting drain upon the germinal epithelium of another. Desire for paternity, failure to achieve this desire and an increase in the number of sexual attempts are commonly observed to develop into a vicious circle leading to sexual exhaustion and seminal depletion.

DIAGNOSIS OF LEVELS OF GONADAL FUNCTION

This section must consider both the germinal and endocrine functions. The presence or absence of *libido sexualis* cannot be taken as proof of the non-existence or existence of hypogonadism. Rowe (36) wisely observed some years ago:

The chief clinical proponents of the theory of important endocrine activity of the testicle in adult years seem to

have adopted the existence of erectile power and the concomitant ability to indulge in intercourse as the principal if not the sole criterion of normal function. The well-known fact that castration in adult years, for a time at least, leaves the erectile power relatively unimpaired, is resolutely ignored as the only possible method of meeting so obvious a contradiction to their incretory doctrine.

Endocrine Levels

Diagnosis of hypogonadism (androgenic deficiency) must consider these objective data: size and consistency of gonads; anatomic state of penis and scrotum; condition of prostate and seminal vesicles; endocrine habitus, including voice, hair distribution and localization of fat; roentgenologic findings, especially epiphyseal status; anthropometric measurements; androgenic titers of urine; and blood chemistry studies, especially in regard to sodium, potassium and chloride metabolism (37).

Grave loss of androgenic function results in marked alterations in the accessory sexual organs, the severity of which is determined largely by the time in which the deficiency becomes apparent, i.e., whether it appears before or after puberty, and the resultant effects upon skeletal structure. The effects of a hypogonadism which occurs during pre-adolescent and adolescent years are grave. Due to retardation of epiphyseal closure, the individual usually grows tall and is slight of build. The lower measurement comes to exceed the upper and the span surpasses the height. Sexual maturation fails to occur. Axillary, pubic, limb, facial and trunk hair do not appear and the voice remains childlike. The external genitalia and prostate gland remain hypoplastic. Muscular growth is poorly defined, the small, flabby musculature suggesting feminine development. The skin is fine, smooth and boyish, but ages rapidly. Localized depositions of fat about the hips, pubes and breasts may be associated but more often are absent. Distinct personality changes are often manifested in the form of shyness, effeminate and retiring disposition and lack of aggressiveness and bodily strength. The basal metabolic levels may be depressed moderately to −20 or −25 per cent. Seminal failure is absolute.

The onset of marked androgenic failure of the testes after adolescence produces less striking changes. The various secondary sexual characteristics tend to regress but the skeletal structure is unaffected. The penis, scrotum and prostate become slightly smaller. The growth of hair on the face, chest, extremities, axilla and pubes may diminish but complete loss is usually not noted. Moderate elevation of the pitch of the voice may result. The *libido sexualis* may be diminished but is not wholly absent. Sexual ability is retained to some degree. Pronounced decrease in the masculine aggressiveness, muscular strength and ambition results in the development of a rather placid individual. Vasomotor phenomena suggestive of the climacteric disturbances in women may occur.

The effects of moderate androgenic deficiency are determined likewise by the time of onset, i.e., whether before or after adolescence. Seminal failure is usually severe, erections being occasional in appearance, the seminal fluid scanty and containing few if any spermatozoa.

Androgens. Studies of the urine of males with hypogonadism have been instituted with hopes that the detection of significant alterations in the levels of excretion of androgenic substances would permit a quantitative expression of the gonadal function. This hypothesis has not been supported by the clinical data available. The conflicting data may be reviewed briefly.

The studies of McCullagh, Cuyler and Frawley (38), McCullagh, McCullagh and Hicken (39), McCullagh and Renshaw (40), Kochakian (41) and Feinier and Rothman (42) disclosed no androgenic substances in the urine of male castrates. Later investigations, in which were employed improved methods of extraction and bioassay, by Bingel (43), Koch (44), Kenyon, Gallagher, Peterson, Dorfman and Koch (45), Chou and Wu (46), Hansen (47), McCullagh, Rumsey and Cuyler (48) and Callow, Callow and Emmens (49) revealed varying amounts of androgenic substances in the urine of male castrates, the average of which was less than the values for normal men. Callow, Callow and Emmens (49) observed that the individual figures for their group of 11 castrates were within the range of variation for normal males. McCullagh and Lilga (50) studied the androgenic titers of 27 patients with hypogonadism, finding that the average values ranged from 0 to low normals. Their average for normal males had been found to be 37.8 I.U. daily. Five of their castrates excreted androgens varying from 0 to 18 I.U. daily. Kenyon, Gallagher, Peterson, Dorfman and Koch (45) observed that the excretion of androgens in their hypogonadal patients averaged about one-third of the values for their normal males (70 I.U. daily); similarly, two castrated males excreted 1 and 3.5 I.U., respectively, of androgenic substances per liter of urine. Similar results were reported by Hoskins, Coffman, Koch and Kenyon (51).

Data on normal individuals are variable. The studies of Talbot, Butler and MacLachlan (52) revealed that the daily excretion of total neutral 17-ketosteroids of children less than 7 years of age was 1.3 mg. but these values increased with age, attaining an average of 4.0 mg. for children between 7 and 12 years of age, and 8.2 mg. for children between 12 and 15 years of age. They observed that the average value of 17-ketosteroids for adult men (15.0 mg.) was slightly higher than that for adult women (10.2 mg.). Dingemanse, Borchardt and Laqueur (53) have observed that boys before the age of puberty excrete 15 I.U. of androgenic substances per liter of urine whereas men

less than 40 years of age show individual variations from 15 to 170 I.U. of androgenic substances per liter of urine, averaging 40 to 50 I.U. per liter.

Qualitative variations in the nature of the androgenic materials recovered from urine have been reported. The studies of Callow (49, 54–56) indicate that the active androgenic substances, androsterone and dehydroisoandrosterone, as well as the inactive androgenic steroid, etiocholanol-3-(α)-17-one, are excretion products of androgenic metabolism found in the urine of both normal and castrated males. The ratio of androsterone to dehydroisoandrosterone in the urine of normal males has been reported to be 1:1 by Butenandt and associates (57–58), Callow and co-workers (49, 54–56, 59) and Dingemanse and Laqueur (60). Employing the technique of capon assay and digitonin fractionation of the pooled urine specimens of two male castrates, which contained 6 I.U. of androgenic substances daily, Hoskins and Webster (61) observed that the ratio of androsterone to dehydroisoandrosterone was 4:1 as compared with the ratio of 1:1 reported above for normal urine. Hansen (47) suggests that the androgenic substance in the urine of male castrates resembles Δ4-androstenedione in its biological action, but Hoskins and Webster (61) attribute this property to the combined activities of androsterone and dehydroisoandrosterone rather than to any biological activity of excreted androstenedione. Callow and Callow (59) found a significant increase in the excretion of transdehydroandrosterone in one castrate, with slight depression of the urinary fractions of androsterone and etiocholanol-3-(α)-17-one. Inasmuch as Crooke and Callow (62) had previously reported an increased excretion of transdehydroandrosterone in the urine of patients with adrenal cortical tumors, this increase in the urinary fraction of transdehydroandrosterone in castrated males has been interpreted to indicate an extra-gonadal origin of the androgen, probably the adrenal cortex. Furthermore, Callow and colleagues (49) have suggested that the increased androgenic output from the adrenals may be compensatory for the absence of the gonads, the higher androgenic levels depressing the increased gonadotropic production of the pituitary; this is comparable to the observations of Hamblen, Ross, Cuyler, Baptist and Ashley (63) in climacteric women. The studies of Dorfman, Cook and Hamilton (64) and Dorfman and Hamilton (65) support the assumption that androgenic compounds may be gonadal or extra-gonadal in origin and that the reduction of testosterone to the various androgenic fractions excreted in the urine may occur in some site other than the testis.

Quantitative and qualitative studies of androgenic substances excreted in the urine of hypogonadal males do not permit the conclusion that diverse grades of testicular failure may be diagnosed or quantified by androgenic determinations.

Estrogens, too, have been recovered from the urine of male castrates by Bingel (43), Eng (66), Hansen (47), Koch (44), Kenyon, Gallagher, Peterson, Dorfman and Koch (45) and Callow and co-workers (67). No comparisons of the estrogenic determinations of the various groups can be made inasmuch as the values for estrogens varied from one-third to 8 times the normal values within the same laboratories. Buxton and Westphal (68) and our group (69) have shown that the male is able to metabolize injected progesterone into the inactive excretion product, pregnanediol. Further studies of estrogenic metabolism in the normal male are necessary before clinical evaluation of alterations in the hypogonadal male is permitted.

Seminal Values

The diagnosis of the level of seminal function may embrace three methods of study, *a*), complete examination of the seminal fluid, *b*), testicular or epididymal aspiration and *c*), testicular biopsy. The first of these studies is a routine part of every fertility survey. The latter two are indicated when azoospermia or marked decreases in seminal values are encountered. The seminal examination considers five factors: *a*), the volume of the seminal fluid; *b*), the number of spermatozoa; *c*), the degree of motility of the spermatozoa; *d*), determination of the relative percentage of normal and abnormal forms; and *e*), an estimation of the viability, i.e., the period of survival of the spermatozoa in seminal specimens.

Volume. The volume of the seminal fluid depends largely upon the quantity of secretion produced by the prostate and seminal vesicles rather than upon the concentration of the spermatozoa, clinical proof of which lies in the fact that post-gonorrheal bilateral epididymitis or bilateral vasectomy (70) produce no significant alterations in volume. Volume of the seminal fluid is increased by continence and decreased by excessive coitus, testicular atrophy, stenosis of the ejaculatory ducts and diseases of prostate and seminal vesicles. Experimentally, decreases in seminal volume have been produced by estrogenic therapy (71).

Depending chiefly on the period of continence, the volume varies considerably among normal men. Meaker (72) noted an average volume of 3 to 6 cc. after one week of continence. Pollák and Joél (73) observed the volume to vary from 3 to 5 cc. in normal men, with an average of 3.3 cc. following a period of continence for 4 to 7 days. Cary and Hotchkiss (74) established the lower limits of normal volume to be 3.5 cc. following a period of sexual rest of not less than 3 days. Hotchkiss, Brunner and Grenley (75) observed the average volume of semen for 200 fertile

men after 72 hours of continence to be 2.3 cc. in condom specimens and 3.12 cc. in withdrawal specimens. Weisman (76) recommends 5 to 7 days of continence and accepts a volume ranging from 2.5 to 5 cc. as being within the normal range.

Spermatozoal count. This affords considerable information concerning seminal function. In general, counts lower than 60,000,000 spermatozoa per cc. or 150,000,000 in the total specimen indicate relatively lowered fertility. It should, however, be appreciated that the seminal count varies normally from time to time in the same individual; therefore, at least two seminal studies are advisable before an opinion concerning the numerical status of the spermatozoa can be formulated. Belding (77) enumerated some of the varied and obscure factors influencing the concentration and total number of spermatozoa as follows: 'Age, frequency of sexual intercourse, relative abundance of prostatic secretion, season, exercise, diet, mental strain, fatigue, functional adequacy of the endocrine glands and debilitating diseases.'

Considerable difference of opinion exists as to the lower numerical limits of fertility. Meaker (72) states that no pregnancies have occurred in his cases in which the total spermatozoal count was less than 60,000,000. Hotchkiss (78) noted a few exceptions in patients with total counts of less than 60,000,000. He reported the average count for fertile males to be 100,000,000 to 150,000,000 per cc. or 400,000,000 to 500,000,000 in the total specimen. Macomber and Saunders (79) observed that the average count for 271 normal and abnormal individuals was 100,000,000 per cc. Hotchkiss, Brunner and Grenley (75) found the average count in 200 fertile men to be 120,630,000 spermatozoa per cc. and 346,020,000 for the total ejaculate. Belding (77) reported 119,000,000 spermatozoa per cc. for a series of fertile matings and 70,000,000 per cc. for a group of sterile matings. Pollák and Joél (73) considered the normal variation ranges from 60,000,000 to 120,000,000 spermatozoa per cc. Discrepancies in the accuracy of spermatozoal counts may be attributed to a personal error of 10 per cent in either direction, in addition to errors in sampling semen, dilution of the fluid, and the method used (76).

Hamblen (80), citing the error of accepting any strict criteria for seminal normalcy, has reported interesting data regarding the seminal findings in husbands of barren couples eventually attaining parenthood, the studies reported being those closest related temporally to the occurrence of pregnancies. The average composite values for the seminal fluid of the group were, *a*), volume, 4 cc.; *b*), abnormal forms, 37 per cent; *c*), motility, 58 per cent; and *d*), count 101,000,000. The range of values for individual specimens was as follows:

Volume	1 to 8 cc.
Abnormal forms	14 to 67 per cent
Motility	8 to 95 per cent
Number of spermatozoa per cc.	2,000,000 to 249,000,000

Motility. Numerous observers believe the optimum degree of motility of spermatozoa to be above 80 per cent, although Cary and Hotchkiss (74) have observed a state of relative fertility in their patients manifesting spermatozoal motility as low as 25 per cent. Weisman (76) has pointed out, however, that seminal specimens should not be examined earlier than 45 minutes, in order to permit liquefaction to take place, or later than 3 hours.

More attention should be paid, perhaps, to the kind of motion exhibited by spermatozoa rather than being satisfied with the fact that they are motile. Five kinds of motions have been described (72); *a*), progressive vibratile; *b*), undulatory tactile; *c*), stationary bunting; *d*), rotary swimming; and *e*), pendulum swimming. The latter two kinds of motion have been considered abnormal.

Decreased motility (76) may be the result of either external or internal factors. The external factors include *a*), various contaminants in the receptacle, such as spermatocidal chemicals; *b*), extreme heat; or *c*), tap water (81). The internal causes include *a*), sexual exhaustion with resultant formation of immature spermatozoa; *b*), various lesions of the genito-urinary tract ascribable to gonorrheal infection; orchitis following mumps; and *c*), toxic depression of the germinal epithelium by chemical factors, such as drugs and metals (76). Charny (70) stresses that necrozoöspermia is usually associated with oligozoöspermia and poikilozoöspermia. The finding of necrozoöspermia alone, according to Charny, focuses attention upon the toxic adnexal secretions rather than endocrine failure of the testes.

Spermatozoal morphology. This is considered by most investigators to offer the greatest amount of information concerning germinal adequacy. Meaker (72) has observed that the abnormal forms are less than 15 per cent in highly fertile men but as high or higher than 40 per cent in individuals of lowered fertility. The studies of Moench (82) revealed that the abnormal forms in fertile men rarely exceeded 20 per cent and that, if a higher percentage of abnormal spermatozoa existed, sterility and abortion followed commonly. It is accepted generally that the presence of excess numbers of abnormal spermatozoa represents defective spermatogenesis.

Abnormal forms represent, in general, spermatozoa which do not conform to the general appearance of average spermatozoa. The abnormalities of morphology may be manifest in the head, the body or the tail. In general, abnormal forms may represent immature spermatozoa, characterized by an excessive

amount of cytoplasm around the head or body and usually a rudimentary tail (70), or degenerated spermatozoa, in which alterations of structure are so numerous as to defy description.

Spermatozoal viability. Although it is agreed generally that a definite attribute of healthy spermatozoa is the ability to remain motile for considerable time at an optimum temperature, the significance of asthenozoöspermia, other than confirmatory evidence of pathologic spermatogenesis, remains obscure.

Considerable variation in statements concerning the viability of normal spermatozoa exist. Cary and Hotchkiss (74) believe spermatozoal activity should be present at the end of 5 or 6 hours. Belding (83) states that the majority of spermatozoa may endure at room temperature for 30 to 32 hours and at body temperature for 23 hours. Moench (84) observed that most spermatozoa maintained at body temperature for 18 hours died. Meaker (72) reported a case in which pregnancy occurred from spermatozoa the viability of which did not exceed 8 hours. Weisman (85) concludes that spermatozoa that do not endure incubation at 37.5° C. for at least 12 hours or survive at room temperature for 24 hours may be considered pathologic.

When severe seminal impairment is indicated by seminal analysis, histologic studies of the germinal epithelium secured by testicular biopsy affords considerable information concerning the functional activity of the seminiferous tubules. In this manner obstructive lesions along the ducts of egress of the spermatozoa may be differentiated from primary failure of the germinal elements.

SUMMARY

When a diagnosis of hypogonadism or seminal failure without androgenic failure has been established, search must then be made for the various etiologic factors responsible for these gonadal alterations before the prognosis may be determined or rational therapy be instituted. The segregation of the various causative factors is not always easy. Testing with either stimulating or substitution endocrine substances may form a part of the diagnostic effort.

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Clinical Determination of Pregnanediol Excretion

[A Review Article]

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PREGNANEDIOL was one of the earliest of the sex steroids to be isolated from human pregnancy urine (1) and characterized (2). It was found to be physiologically inert, and was ignored by biologists and clinicians for several years. To the steroid chemists it was of interest as a possible inactive excretion product of an active precursor. Butenandt, in 1934 (3), oxidized pregnanediol to progesterone. This not only showed the close chemical relationship between the two steroids, but was the first synthesis *in vitro* of the active principle of the corpus luteum.

Demonstration of the biological relationship between pregnanediol and progesterone, as well as the correlation of the level of corpus luteum activity with the excretion of pregnanediol had to await a semi-quantitative, semi-micro method for the determination of pregnanediol. Venning and Browne did the preliminary work for this with their isolation, in 1936, of a water-soluble pregnanediol complex from human pregnancy urine (4). Venning later modified the isolation procedure slightly to give a method applicable to the routine determination of small amounts of sodium pregnanediol glucuronidate, one of the excretory forms of this steriod.

That this method filled a manifest need is apparent from the work that has been reported in which it was employed. The information obtained from its use by the originators and other investigators can be briefly summarized as follows. From 10 to 30 per cent of administered progesterone can be recovered from the urine as sodium pregnanediol glucuronidate. In the course of a normal menstrual cycle from 3 to 50 mg. of pregnanediol can be isolated, this excretion starting soon after ovulation and the formation of the corpus luteum, rising to a maximum about one week before the next bleeding, and falling off to zero before flow starts. In a normal pregnancy, excretion of pregnanediol remains at the level characteristic of the menstrual cycle for about 8 weeks, then rises until it reaches 100 to 150 mg. per diem by the 38th week, and falls off until the initiation of labor. In cases of menstrual irregularities, complicated pregnancies, or, in common with the other urinary sex steroids, hepatic or renal dysfunction, the excretion will be altered, usually to a lower level.

A multiplicity of methods confronts the investigator who wishes to determine the level or presence of corpus luteum activity. The most direct evidence of corpus luteum function is the well-developed progestational change in the endometrium. Samples of this tissue may be obtained for examination by either curettage or biopsy. Neither of these procedures can be repeated too frequently. Furthermore, the information they give is qualitative in nature, making it difficult to determine the level of activity. More quantitative information can be obtained from the determination of pregnanediol excretion.

The most widely used method for determining this is the classical one of Venning (5). The glucuronidate is extracted from the urine by shaking several times with butanol. After evaporation of the solution in vacuo, and re-dissolving the residue in alkali solution, the complex is precipitated with acetone. The precipitate, after final purification, is determined by weighing, and identified by its melting point and mixed melting point with a known pure sample.

There are two major disadvantages to this method, which have been responsible for two major developments in the analysis. One of these is the difficulty of checking the identity and purity of the final precipitate. All too frequently specimens of urine obtained during the luteal phase of a cycle will yield amorphous precipitates of less than 5 mg. Amorphous compounds have no fixed melting points, so that their identification by this method is unsatisfactory and inconclusive. This difficulty has led to work on the determination of the glyconuronic acid content of the precipitate (6, 7). These procedures determine the reducing activity of the precipitate before and after hydrolysis, measuring this with an alkaline copper reagent either colorimetrically or titrimetrically. If the Venning method is used, some such form of glycuronic acid analysis should be employed to check small and dubious precipitates. The colorimetric method of Maughan, Evelyn and Browne (8) for the direct determination of glycuronic acid or sodium

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pregnanediol glucuronidate, by condensation with aquaeous naphthoresorcinol may also be employed.

The other major disadvantage is inherent in the determination of pregnanediol as its glucuronidate. It is not definitely known, as yet, whether all pregnanediol excreted is conjugated with glycuronic acid. More troublesome, practically, is the instability of the conjugated glycuronidate, which hydrolyzes readily at room temperature. This characteristic necessitates special care in chilling the specimen immediately after voiding, and analyzing the urine within 15 hours of collection (9). Since it is the complex that is determined, hydrolysis will cause the results to be low or negative. Technically, extraction by shaking with butanol is tedious; design of a continuous extractor to handle this solvent is difficult, since butanol is particularly prone to form emulsions with urine.

Two radically new methods overcome these difficulties. They employ simplified extraction procedures, and determine the relatively rugged molecule of pregnanediol instead of its fragile complex. One of these is the method of Astwood and Jones (10) which combines hydrolysis with extraction by refluxing the acidified urine with toluene. After purification and evaporation of the toluene extract, the steroid is dissolved in ethanol and precipitated from this solution with alkali. This precipitate is recrystallized, transferred to ethanol, and the solution evaporated and weighed. Purity of the precipitate is checked by its melting point.

A modification of this method is that of Talbot, Berman, MacLachlan and Wolfe (11), which is especially useful when a 17-ketosteroid determination is to be made on the same specimen. The urine specimen is hydrolyzed and extracted with any steroid solvent in a continuous extractor designed for it. The crude neutral fraction of the extract is treated with Girard's Reagent "T" which separates the ketonic and non-ketonic fractions by reacting with ketone groups to give water-soluble compounds. A toluene solution of the water insoluble, non-ketonic fraction of the extract, which contains the pregnanediol, is purified by the method of Astwood and Jones. Final assay is made either gravimetrically or colorimetrically by treating the steroid with sulfuric acid. This is a Salkowski reaction, and is the simplest of the general steroid color reactions; addition of acetic anhydride to this makes it the Lieberman reaction which is commonly used for the determination of cholesterol. The use of one of the non-specific steroid color reactions on a precipitate which, by reason of the isolation procedure, contains chiefly pregnanediol is at least as accurate as weighing a precipitate of indeterminate composition, and may prove more rapid for routine use, as well as indicating the steroid content of the precipitate.

Methods of determining pregnanediol are, at present, in a state of flux. Those who are among 'the last to cast the old aside' will continue to use the Venning method. With extreme care in collection and handling of the urine, this method, with ancillary glycuronic acid analysis, even though cumbersome and ill-adapted to routine use, will give results which are unlikely to be questioned. 'The first by whom the new is tried' will find that the newer procedures which determine the molecule as a steroid, and not as a glycuronidate, as far more flexible and better adapted to routine use.

The ideal clinical method for determining pregnanediol has yet to be published. It must be adapted to routine use, since the number of cases of menstrual irregularity encountered in clinical endocrinology is large, and the determinations needed for each patient are many. The compound chosen for analysis should be stable in order to make routine collection practical for outpatients. The method should be sensitive to at least a milligram, and accurate to half of that. The terminal reaction should be unique for pregnanediol, so that the pregnanediol content of the precipitate will be known.

All of the methods mentioned above have some of these features, none has all of them.

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Disposal of Glucose at High and Normal[1] Blood Sugar Levels under Action of Insulin

[Diabetes Mellitus]

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IT IS OF PRACTICAL IMPORTANCE in the treatment of diabetic patients to know if there is a difference in the rate of disappearance of glucose under the action of insulin at different blood-sugar levels. Our interest in this problem was aroused during routine observations on diabetic patients. We observed a patient on insulin with the blood sugar in the normal range who did not excrete the extra glucose ingested when placed on a high carbohydrate diet with the same insulin dose. The latter regime was associated with a high blood-sugar level and the result was similar to that which has been reported by others (1, 2, 3).

This paper summarizes the results of a study of the disposal of glucose at normal and high blood-sugar levels under the action of the same amount of insulin. The study was made on depancreatized animals as well as diabetic patients.

METHODS

The scheme of experiment employed in the diabetic patients and the depancreatized dog and rabbit were essentially the same. At least two series of observations were made in each case, *a*) with the blood sugar kept within the normal range for 3 to 6 hours with a given dose of insulin and *b*), with the blood sugar maintained at a high level (300–600 mg. per cent) for 3 to 6 hours with the same dose of insulin. Glucose in physiological saline was given as a constant intravenous drip with the amount required per hour to maintain the desired blood-sugar level regulated by frequent blood-sugar determinations. The total urinary sugar output was measured in all cases. The animals were catheterized and the bladder washed out at the beginning and end of the test periods. As the interval during which the blood sugar was maintained at a constant level did not always correspond exactly with the times of catheterization, or in the case of patients, urination, the amount of sugar excreted in the urine was adjusted to the blood-sugar periods.

Blood-sugar determinations were made on venous blood by the micro Folin-Wu method. Urine sugar was determined by the quantitative Benedict method. Glycogen determinations were performed by the Pflüger method. Nembutal anesthesia was used in the animal experiments.

The diabetic patients used had no serious complications and were in good condition and the diabetes was under control at the time of study.

When the blood-glucose concentration is not kept relatively constant in balance studies of glucose utilization, elaborate calculations are necessary to compute the amount of sugar in the body fluid. Various workers use different figures for the amount of interstitial fluid; and, more important, the glucose balance between interstitial and intracellular fluid is uncertain. Since corrections are always open to question, an attempt was always made to keep a relatively constant blood-sugar level. At the high blood-sugar levels this ideal was not always obtained. However, if the blood-sugar level was lower at the end of a test than at the beginning, it is obvious that more glucose could have been disposed of than the amount tabulated and corrections are not essential in such cases. As will be evident from our results this constitutes an *a fortiori* argument in favor of our conclusions.

RESULTS

Patients. The results obtained on 4 diabetic patients are summarized in table 1. Figures 1 and 2

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[1] Normal blood sugar is used to indicate a blood-sugar level within the physiological range (80–140 mg.%).

TABLE 1. GLUCOSE DISPOSAL AT HIGH AND NORMAL BLOOD-SUGAR LEVELS IN DIABETIC PATIENTS[1]

	Patients	Duration of Experiment	Regular Insulin Subcut., U	Blood-Sugar Levels, mg. %		Glucose Intravenously, gm.	Glucose in Urine,[2] gm.	Glucose Retained gm.
				Initial	Final			
1.	A.S., male, 57; diet C 175, P 70, F[3] 80	5 hr., 47 min.	10	592.4	482.0	255.0	106.00	149.00
	R.I.[4] 10–10–5	5 hr., 40 min.	15[5]	120.5	125.0	38.2	0	38.20
2.	N.S., female, 14; diet C 150, P 65, F 80	6 hr.	20 C.I.	540.0	430.0	249.5	98.00	151.50
	C.I.[6] 30–20–20	5 hr. 30 min.	20 C.I.	142.8	129.8	52.78	3.67	49.11
3.	S.J., female, 13; diet C 200, P 75, F 80	4 hr. 46 min.	10	452.0	384.0	178.0	48.20	129.80
	R.I. 15–0–10							
	PZI:[7] 30	4 hr.	10	81.3	85.1	34.9	0	34.90
4.	F.F., male, 36; diet C 175, P 70, F 80	4 hr.	10	551.6	551.6	217.9	82.00	135.90
	Insulin 25–10–25–10	6 hr. 4 min.	10	140.8	149.2	57.0	1.50	55.50

[1] Patients fasting throughout test.
[2] Aliquot samples on urine.
[3] C, Carbohydrate; P, Protein; F, Fat.
[4] R.I., regular insulin.
[5] 10 U 6:40 A.M. } Test started 8:30 A.M.
5 U 9:05 A.M. }
[6] C.I., crystalline insulin.
[7] PZI, protamine zinc insulin.

show the record of one patient (*patient S. J.*, number 3, table 1) in detail to illustrate how the results tabulated in table 1 were obtained. The time period included in the graphs is longer than that given in the tables since the period used in the tables was made between two points where the initial and final blood-sugar levels were approximately the same. The graphs show a longer period since they include the time required to bring the blood sugar to the normal level in one instance and to raise it to a high level in the other. A striking increase in glucose disposal at high blood-sugar levels occurred: Three and .7 times as much sugar disappeared under the action of insulin at the high blood-sugar level in *patient S. J.* as at the normal level. This figure varied from 2.4 to 3.7 for different patients. The patients included two moderately severe juvenile diabetics and two milder, older diabetics.

Depancreatized animals. The results on 4 depancreatized dogs are summarized in table 2. Figures 3 and 4 are the detailed study of one dog (*dog D*, number 3, table 2) and illustrate the method by which the results in table 2 were obtained. (A slightly longer time period was included in the graphs than in the table as explained above.) In 3 dogs, 1.6 to 2.6 times as much glucose disappeared under the action of insulin at the high blood-sugar level as at the normal level. The utilization rate calculated as grams of glucose retained per kilogram per hour showed a marked difference between the high and normal blood-sugar level. At the high blood-sugar level with insulin the rate varied in the different dogs from 0.60 gm. per kg. per hour to 2.63 gm. per kg. per hour, with an average of 1.20 gm. per kg. per hour. At the normal blood-sugar level the rate varied from 0.25 gm. to 0.76 gm., with an average of 0.52 gm., per kg. per hour. In one dog (*dog S*, number 2, table 2) there was no difference in glucose disposal at high and norma levels. As this dog died it was not possible to check the determinations. Duplicate runs at both high and normal levels with insulin were made in *dog D* (table 2) with a difference of less than 8 gm. between the

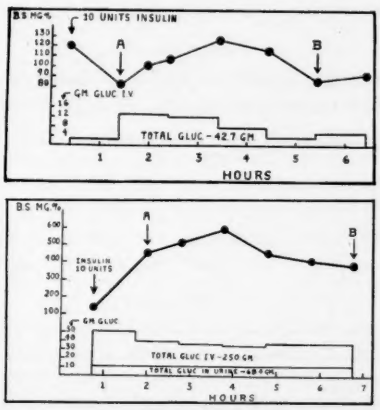

FIG. 1, (*upper*). DISPOSAL OF GLUCOSE AT A NORMAL BLOOD-SUGAR LEVEL WITH INSULIN IN PATIENT S. J. Patient fasting throughout test. No sugar in urine. Arrows *A* and *B* indicate period of test used in calculation of glucose disposal as recorded in table 1 (see text). *Abbreviations:* B. S., blood sugar; Gluc., glucose; I. V., intravenous. FIG. 2, (*lower*). DISPOSAL OF GLUCOSE AT A HIGH BLOOD-SUGAR LEVEL WITH INSULIN IN PATIENT S. J. Arrows *A* and *B* indicate period of test used in calculation of glucose disposal as recorded in table 1 (see text).

determinations for the normal level and 3 gm. at the high level.

The results on 4 depancreatized rabbits are tabulated in table 3. In many respects these results were unsatisfactory. Large amounts of insulin were required in these animals, due to a phase of relative insulin resistance. Also, it was difficult to prevent

TABLE 2. GLUCOSE DISPOSAL AT HIGH AND NORMAL BLOOD-SUGAR LEVELS IN DEPANCREATIZED DOGS[1]

Dog	Weight kg.	Duration of Experiment	Regular Insulin, I.V.[2] U	Blood-Sugar Levels, mg %		Glucose I.V., gm.	Glucose in Urine, gm.[3]	Glucose Retained, gm.	Glucose Utilized, kg. gm./hr.
				Initial	Final				
1, *R*	?	4 hr., 56 min.	10	380	296	68.90	19.80	49.10	?
	7.27	5 hr. 53 min.	10	221	250	30.25	0.60	29.65	0.69
2, *S*	9.9	6 hr., 8 min.	10	500	472	72.47	56.50	15.97	0.26
	10.4	7 hr., 5 min.	10	125	122	18.50	0	18.50	0.25
3, *D*	6.7	4 hr., 48 min.	10	412	380	59.70	14.70	45.00	1.40
	6.8	5 hr., 56 min.	10	570	433.3	69.17	26.20	42.97	1.06
	6.5	6 hr., 55 min.	12	75	88	19.90	0	19.90	0.43
	8.2	5 hr., 32 min.	10	77	82	27.50	0	27.50	0.60
4, C	5.45	4 hr., 23 min.	0	457	420	27.80	21.40	6.40	0.31
	5.22	4 hr., 3 min.	10	534	500	45.00	19.40	25.60	1.62
	5.22	4 hr.	10	154	156	15.80	0.37	15.43	0.76
	4.25	6 hr.[4]	30	74	66.5	13.10	0.39	12.71	0.50
		3 hr.[4]	20	381	384	41.80	8.13	33.67	2.63
5, *N.D.*	8.57	4 hr., 30 min.	20	500	512	40.60	16.80	23.80	0.60

[1] Dogs fasting throughout test.
[2] I.V.—intravenously.
[3] Aliquot samples on urine.
[4] Tests run same day in sequence.

some wide fluctuations of the blood sugar. A definite difference, however, in glucose disposal at high and normal blood-sugar levels is seen with increased glucose disposal at high blood sugar levels.

DISCUSSION

It is obvious from the results tabulated here that far more glucose disappeared at high blood-sugar levels than at the normal level with the same amount of insulin. The results given all represent glucose disposal under the action of insulin. Soskin (4) has reported glucose disposal rates in the acutely eviscerated animal at high blood-sugar levels but without insulin. He gives a utilization rate of 410 mg. of glucose per kg. per hour with a blood-sugar level of 285 mg. per cent. This is a lower rate than we obtained with high blood-sugar levels in depancreatized dogs with insulin in which the average rate was 1200 mg. per kg. per hour. In one dog (*dog C*, No. 4, table 2) which was observed at a high blood-sugar level both with and without insulin the utilization rate was 0.3 gm. without insulin, contrasted with 1.62 to 2.63 gm. per hour with insulin.

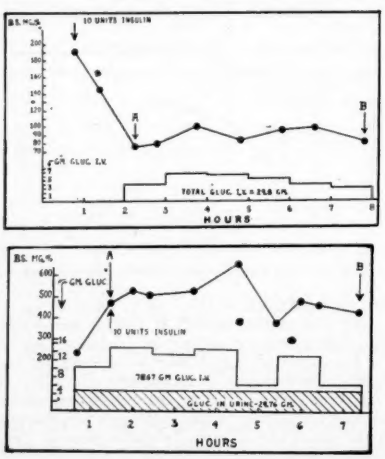

FIG. 3, (*upper*). DISPOSAL OF GLUCOSE AT A NORMAL BLOOD-SUGAR LEVEL WITH INSULIN IN DEPANCREATIZED DOG *D*. Depancreatized *dog* 3 (table 2), weight 8.2 kg.; dog fasting throughout test. No sugar in urine. Arrows *A* and *B* indicate period of test used in calculation of glucose disposal as recorded in table 2 (see text).
FIG. 4, (*lower*). DISPOSAL OF GLUCOSE AT A HIGH BLOOD-SUGAR LEVEL WITH INSULIN IN DEPANCREATIZED DOG *D*. Depancreatized *dog* 3 (table 2), weight 6.8 kg. Dog fasting throughout test. Arrows *A* and *B* indicate period of test used in calculation of glucose disposal as recorded in table 2 (see text).

The mechanism and site of action of the increased disposal of glucose at high blood-sugar levels in comparison with normal levels with the same dose of insulin is not clear. In patients an increased secretion of endogenous insulin may account for increased glucose disposal at high blood-sugar levels. This could hardly be the major mechanism, for similar results were obtained in completely depancreatized animals although the percentage increase in glucose disposal at high blood-sugar levels was less than in the diabetic patients. De Nayer et al. (5) believe that the liver is the organ that disposes of glucose under insulin action in the normal blood-sugar range. They found that the normal dog with the maximal insulin effect disposed of 1.30 gm. of glucose per kg. while the hepatectomized animal utilized only 0.35 gm. of glucose per kg. whether with or without insulin. Whether this is true at high blood-sugar levels has not been determined.

Cori and Cori (6) accounted for 95 per cent of the glucose given to rats with 15 U of insulin and a blood-sugar level of 77 mg. per cent by oxidation or glycogen storage in a test period of 4 hours. Best, Hoet, and Marks (7) in the eviscerated spinal cat also accounted for most of the glucose given with 30 U of insulin and a blood-sugar level between 440 and 510 mg. per cent over a period of 3.5 hours by glycogen increase and oxidation. In contrast to this previous work we are unable to account completely for the glucose disposed of at high blood-sugar levels by glycogen increase in liver and muscle and by oxidation.

glycogen of two depancreatized dogs and one depancreatized rabbit actually decreased at high blood-sugar levels with insulin. This is in distinct contrast to the idea which is prevalent that there is an increase in liver glycogen with insulin action at high blood-sugar levels.

The study reported here is of practical importance in the clinical control of diabetes. It should be recognized by those using insulin that the ingestion of additional carbohydrate leading to a high blood-sugar level with the insulin kept the same does not lead to the excretion of all of this extra carbohydrate. When

TABLE 3. GLUCOSE DISPOSAL AT HIGH AND NORMAL BLOOD-SUGAR LEVELS IN DEPANCREATIZED RABBITS[1]

Rabbit	Weight kg.	Duration of Experiment	Regular Insulin I.V., U	Blood-Sugar Levels, mg. %		Glucose I.V., gm.	Gluc.[2] in Urine, gm.	Gluc. Retained gm.	Glycogen,[3] gm.			
				Initial	Final				Liver		Muscle	
									Initial	Final	Initial	Final
1	1.5	6 hr. 17 min.	30	317	326	7.85	4.38	3.47	2.47	2.78	0.08	0.18
2	1.73	4 hr. 13 min.	30	534	500	5.85	3.38	2.47	0.32	0.65	0.23	0.47
3	1.82	4 hr. 28 min.	30	364	303	7.65	1.41	6.24	1.13	0.75	0.1	0.15
4	0.97	1 hr. 25 min.	60	75.5	84	0.72	0	0.72	0.31	0.72	0.11	0.05

[1] Rabbits fasted 1–2 days before test and during test.
[2] Aliquot samples on urines.
[3] Slight difference in time factor on biopsies and blood sugar levels.

In *dog ND* (table 2) the muscle glycogen decreased from 0.32 to 0.27 per cent during 4.5 hours with a blood-sugar level between 500 and 512 mg. per cent. In *dog C*, weight 4.25 kg. (table 2), 33.67 gm. of glucose was disposed of under the action of insulin at a high blood-sugar level. Only 10.3 gm. of this could be accounted for as increased muscle glycogen. (Muscle glycogen increase was 0.46 per cent.) The liver glycogen decreased during the same period from 5.03 to 4.55 per cent.

In one depancreatized *dog ND* (table 2) oxygen consumption was measured twice during the test with elevated blood sugar. In each instance the oxygen consumption was 2.48 liters per hour or 11.16 liters for the 4.5 hour test period. The 23.8 gm. of glucose utilized would have required 17.78 liters of oxygen (1 gm. of glucose is oxidized by 747 cc. of oxygen). As noted above there was a decrease in both liver and muscle glycogen during the same period in this dog.

In the depancreatized rabbits similar results were obtained. The glucose which disappeared could not be accounted for by liver or muscle glycogen increase (table 3). The fate of this glucose, which cannot be accounted for in balance studies, is not known. Possibilities which should be explored are conversion to other intermediary carbohydrate compounds or to fat.

We were impressed with the fact that the liver insulin action and carbohydrate are not balanced at high blood-sugar levels due to excess carbohydrate there is a compensating mechanism which acts usefully to dispose of more glucose. This fact re-emphasizes the futility of simple insulin-carbohydrate ratios. These ratios differ from patient to patient and, as we have shown here, vary in the same patient with changing blood-sugar levels, the ratio increasing at the higher levels.

CONCLUSIONS

1. In 4 diabetic patients, 3 depancreatized dogs and 3 depancreatized rabbits more glucose disappeared under the action of insulin at a high blood-sugar level than at the normal physiological level. The fact should be stressed that this difference occurred with insulin and possibly may not occur without insulin.

2. The glucose which disappeared at high blood-sugar levels with insulin could not be fully accounted for by increased liver or muscle glycogen or by oxidation. The liver glycogen in the depancreatized animals actually dropped at the high blood-sugar levels.

3. These results are of importance clinically since they show that there is not a strict overflow mechanism at high blood-sugar levels with insulin because of an increased insulin-carbohydrate ratio at such levels.

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Insulin Allergy

A Report of Eight Cases with Generalized Symptoms

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THE PROBLEM OF INSULIN ALLERGY has been discussed by Tuft (1), Allen and Scherer (2), Herzstein and Pollack (3), McDaniel (4), and among others and most recently by Harten and Walzer (5) and by Yasuna (6).

Definition. The terms insulin sensitivity and hypersensitivity have been used frequently as synonyms for allergy, but they also have been applied to describe the rapid and excessive hypoglycemic response to insulin in contradistinction to insulin resistance or insensitivity. In this sense, sensitivity differs from allergy completely, not only in symptomatology but also in its mechanism. It may occur with or without allergic symptoms. An attempt should be made, therefore, to differentiate these two conditions in their terminology. In this paper we propose to use the term 'allergic' as referring to symptoms which are due to the antigenic property of insulin as a protein substance (7) and to speak of sensitivity and insensitivity as referring to the varying degrees of body response to the specific metabolic function of insulin as a hormone.

Symptomatology. About 20 per cent of all persons treated with insulin have been reported to show mild and transient local allergic reactions (2, 4, 5). Within a week or 10 days after the beginning of treatment swelling and erythema which persist for 30 minutes to several hours will occur at the site of injection. Itching and induration may be present. Usually these reactions will not interfere with the action of insulin as such and they will disappear without special care after a period of 10 days or 2 weeks. Sometimes changing the brand of insulin may be helpful.

In a few patients, however, the local reactions increase in severity, extend in size and spread over the body causing generalized urticaria with involvement of the mucous membranes, with severe pruritus, joint pain, headaches, elevated temperature, and circulatory and gastro-intestinal symptoms. These reactions usually develop slowly over a period of several hours and may persist for more than one day. They do not subside spontaneously with the continued use of insulin, but require desensitization or the cessation of insulin treatment.

These generalized allergic reactions after insulin are rare. Harten and Walzer (5) have found about 200 case reports in the world literature between 1923 and 1940 but in many of these there was insufficient evidence that the characteristic symptoms were due to the insulin protein itself rather than to nonspecific animal proteins, pancreas extract or preservatives present in the insulin preparations. Yasuna (6) in his critical review accepted only 11 cases from the literature as proven generalized insulin allergy and added one case of his own. In the meantime 3 more cases have been reported, 2 by Herzog (8) and one by Hinko, Fenton and Balberor (9). Satisfactory immunologic tests have been possible only since crystalline insulin has become available. Cannon and Marshall (10) have described a new insulin-precipitation test which will be of help, in addition to the commonly used intradermal skin tests and the passive transfer test of Prausnitz and Kuester.

CLINICAL PROCEDURE AND OBSERVATIONS

The purpose of this paper is to report observations on generalized insulin allergy in 8 patients who were studied in the Metabolism Clinic of the Billings Hospital of the University of Chicago during the years 1937 to 1941.

These patients either had developed clinical symptoms of insulin allergy during observation in our clinic or were referred to us because of their symptoms.

In each of these patients the diabetic and allergic histories were taken carefully and all or several of the following tests were performed.

Insulin skin tests. Five-hundredths of a cc. of U 40 regular, protamine zinc and commercial crystalline insulin of different brands and origins (beef or pork) were injected intradermally. In 5 patients tests were

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TABLE 1. CLINICAL FINDINGS AND OBSERVATIONS IN 8 PATIENTS WITH GENERALIZED INSULIN ALLERGY

Case No.	Sex, Age	Clinical Diagnosis	Duration of Diabetes, years	Allergic History	Insulin allergy					Eosinophilia %
					Onset			Symptoms		
					During first Treatment	After lapse of Treatment	Time before first symptoms	Local	General	
1, *L.H.*[1] 169663	Female, 70	Diabetes mellitus; cancer of breast; hypertensive heart disease; osteoarthritis	8	None	+	0	2 wk.	Swelling, redness, itching, induration, erythema	Urticaria, esp. in face; pruritus, nausea, vomiting	2
2, *R.A.*,[1] 193284	Female, 63	Diabetes mellitus; arteriosclerosis	5	Developed allergy against fresh fruit after insulin allergy; son: hay fever		+	9 days	swelling, redness, itching, induration, erythema	urticaria, pruritus, swelling of mucus membranes, joint pain, headache, nausea, vomiting, fever	1–5
3, *W.B.*,[1] 253200	Male, 51	Diabetes mellitus; arteriosclerosis	12	None		+	immediately	swelling, redness, itching, induration, and erythema	urticaria, pruritus, joint pain, fever	4
4, *E.S.*, 259591	Female, 63	Diabetes mellitus; arteriosclerosis; obesity	1	Was allergic against cat hair when younger	+	0	1–2 wk.	swelling, redness, itching, induration, and erythema	joint pain	2
5, *H.L.*,	Male, 56	Diabetes mellitus	2	None		+	1 wk.	itching, swelling	urticaria, swelling of mucus membranes, pruritus	2
6, *A.L.*, 252684	Female, 56	Diabetes mellitus; arterial hypertension	6	None		+	immediately	itching, redness, swelling	headaches, joint pain, fever	2–5
7, *H.L.*,[1] 33205	Male, 52	Diabetes mellitus; diabetic neuritis; arteriosclerotic heart disease; optic atrophy; old retinitis; complicated cataract	14	None	+		1 wk.	itching, swelling, redness, erythema	urticaria, pruritus	3
8, *H.CH.*, 141438	Male, 55	Diabetes mellitus; general arteriosclerosis; angina pectoris; pyonephrosis; otitis media	2	None	+		11 days	itching, swelling, redness, erythema, (persistent for several days), induration	urticaria, headaches	5–13

[1] The histories of *cases* 1, 2, 3 and 7 reported in this paper.

[2] Himsworth's test for insulin sensitivity was made in *cases* 2, 3, 4, 6 and 8. In *cases* 1 and 7 insulin sensitivity or insensitivity was proven by clinical observation.

TABLE 1. CLINICAL FINDINGS AND OBSERVATIONS IN 8 PATIENTS WITH GENERALIZED INSULIN ALLERGY

Skin Tests					Precipitation Test	Passive Transfer Test	Insulin		Therapy	Remarks
Crystalline Insulin	Regular Insulin	Protamin zinc Insulin	Human Insulin	Controls			Sensitive[2]	Insensitive		
2+	4+	3+	−	−	negative		+		Desensitization with frequent small doses of crystalline insulin; intramuscular injections attempted, both partly successful	Patient died of pneumonia in diabetic ketosis; autopsy
2+	3+	3+	4+	0	negative	positive	+		Desensitization with frequent small doses; i.m. injections attempted, both unsuccessful; control on diet alone	
4+	4+	4+	3+	0	1:10	positive	+		Intramuscular injections; control on diet alone	
3+	2+	2+	2+	0	negative			+	Control on diet alone	
2+	3+	3+	2+	0		positive	+		Control on diet alone	
2+	3+	3+	−	0	1:5 1:10		+		Intramuscular injections without success; control on diet alone	
2+	3+	3+	−	0	1:80	positive		+	Intramuscular injections	Patient developed severe insulin resistance and required during the last 6 months of his life about 1000 U daily; no autopsy
2+	3+	3+	3+	0	1:10 1:20			+	Control on diet alone	

made also with a special insulin prepared from human pancreas.[1] As controls, normal saline and a 0.5 per cent phenol solution were used. The tests were read after 15, 30, 45, 60 minutes and, in some instances, after 3 and 24 hours. Wheal formation, erythema, induration and pseudopods were observed and measured. Only those tests were described as positive in which wheals and pseudopods developed within 60 minutes after injection. Since positive reactions frequently varied in degree with different types of insulin a grading of 1+, 2+, 3+ and 4+ was used for describing the results (table 1). It should be understood that these grades are relative ones and apply only to test differences in the same patient. They cannot be used to compare degrees of allergic response between different patients.

Passive transfer test (Prausnitz-Kuestner). One-tenth of a cc. of freshly prepared serum of the patient was injected subcutaneously into the forearm of each of two control persons. A similar injection was made with normal serum. Twenty-four hours later 0.05 cc. of crystalline insulin was injected intradermally into the sensitized areas and a non-sensitized area. Again the occurrence of erythema, wheals, and pseudopods was observed.

Insulin collodion-precipitation test (Cannon-Marshall). The tests were performed in Dr. Cannon's laboratory with insulin-coated collodion particles prepared according to the original procedure of the authors (10). The double dilution technique was used, so that the first tube would contain a dilution of serum of 1:5. Then, 0.5 cc. of the insulin-coated particles was added to each tube. Most of the tests were made with unheated sera and with sera heated over a waterbath at 56° C. for 30 minutes. Control tests with crystalline egg albumin-coated particles, normal human sera, uncoated particles and saline were made.

Routine skin tests with the 30 common food and inhalant allergens were performed in the Allergy Clinic (Dr. Harold C. Wagner).

Count of eosinophilic blood cells was made.

The insulin sensitivity test of Himsworth (11) was carried out or other information as to the patient's insulin sensitivity was obtained.

Table 1 gives a comprehensive summary of our findings. The details of four illustrative cases will be found at the end of this paper.

All 8 patients had diabetes and belonged to the middle or higher-age group. Their ages varied between 51 and 70 years, the duration of the diabetes between 1 and 15 years. Three of the patients were males and 5 were females. In 3 instances insulin insensitivity was present, and in one of these (*case 7*) the resistance was so severe that for several months more than 1000 U of insulin daily was necessary to check the hyperglycemia.

Only one patient had an allergic history, while in the families of two others, allergic diseases were known. The routine allergy tests were negative in all patients. An increase of eosinophilic cells was found in one patient only, all others having 5 or less than 5 per cent eosinophiles.

Four patients had had previous periods of insulin treatment, during which no or only mild allergic symptoms had been observed. In two of these patients symptoms appeared immediately after resuming the insulin injections. In the 2 others and in the 5 patients in whom insulin allergy had developed during the first course of treatment, first symptoms were noted not earlier than 7 days and not later than 2 weeks after the beginning of the treatment.

The skin tests with the various brands of insulin and especially with crystalline insulin were positive in all patients. The 5 patients who were tested with human insulin showed positive responses to this preparation also. An immediate reaction with erythema, wheals, pseudopods and itching was observed in all patients. These reactions persisted for several hours and usually reached their peak after 60 minutes or later. In 3 instances this reaction was followed by severe generalized symptoms, with urticaria appearing on the arm or the face (lips and eyelids) and general malaise which persisted for more than 24 hours. The controls were negative or showed an occasional slight erythema which disappeared within one hour.

The passive transfer test was performed in 4 patients and was positive in all instances.

The insulin precipitation test was positive in various degrees in 4 of the 7 patients. The highest titers were found in the blood of a patient who was insulin resistant (*case 7*).

Specific desensitization was successful temporarily in one patient (*case 1*). In another patient (*case 7*) treatment with serum from a rabbit which had been sensitized with the patient's blood, as proposed by Karr (12), was attempted and was unsuccessful. Intramuscular administration of insulin partially alleviated the reactions in some cases and was found to be the best of all therapeutic procedures tried, but it did not completely prevent symptoms. In 6 patients it was finally necessary to discontinue insulin.

Although no patient died from allergic reactions, insulin allergy must be considered as a contributory cause in the death of 1 patient (*case 1*) who died of bronchopneumonia. The symptoms of diabetic acidosis could have been prevented if efficient insulin therapy had been possible. Another patient (*case 7*) died with severe insulin resistance which had developed after the earlier appearance of insulin allergy.

[1] We are indebted for this preparation to Dr. Paul Cannon, for whom it was made by the Eli Lilly Co., Indianapolis, Ind.

Insulin skin tests were carried out in 44 diabetic patients who were treated with insulin but had no symptoms of generalized insulin allergy. Some of them showed mild and transient local reactions as are frequently observed during the second week of treatment with protamine zinc insulin. None showed a complete series of positive tests. In 8 patients protamine zinc insulin alone, and in 6 regular insulin gave positive reactions. These reactions showed wheals but no pseudopods and did not persist longer than one hour.

DISCUSSION

The clinical histories, the positive skin tests with all different brands of commercial insulin, as well as with human insulin and the passive transfer tests seem to prove sufficiently that our patients belong in the group of persons with generalized allergy against the insulin protein itself.[2]

The first question which offers itself is, why are these patients not allergic against their own insulin? None of them was totally diabetic so that the pancreas undoubtedly was still able to produce a certain amount of insulin, yet they were allergic even to injected human insulin. Only speculative answers can be ventured. It may be that the process of extraction alters the insulin molecule, so that even insulin extracted from human pancreas can become an allergen. It may also be that a preexistent allergic disposition is precipitated only if high concentrations of insulin are accumulated subcutaneously. Skin and mucous membranes are the chief organs of allergic response. Under physiologic conditions they are reached by very minute amounts of insulin. This changes if, with the beginning of treatment, insulin depots are placed near the skin. The fact that intramuscular administration of insulin frequently alleviates allergic reactions may point in this direction.

Analysis of our own observations and of those reported in the literature yields certain interesting facts.

Age distribution. The 12 cases with generalized allergic reactions and proven insulin allergy referred to by Yasuna (6) and the 3 cases of Herzog (8) and of Hinko and coworkers (9) belonged to the middle-age group as did our patients. Only one patient was younger than 30, the others were between 40 and 71 years of age. It is possible that this reflects simply the age incidence of diabetes, which is low in the first two decades and increases rapidly later. On the other hand, allergic diseases are known to be very frequent in early life. Although the number of observations is too small to permit statistical conclusions, it is interesting to speculate on the possibility that the tendency toward insulin allergy may be one of the features of diabetes in the middle-age group which differs in so many respects from the diabetes of the juveniles.

Onset of allergic symptoms. Our observations confirm the finding that lapse of treatment seems to be important for the development of insulin allergy. Nine of the 15 cases in the literature had had previous periods of insulin treatment with intervals from a few months to several years. The long interval between the first and second course of treatment seems to indicate that a sensitization once developed in a predisposed individual will not disappear with time, although a few exceptions have been observed (2, 9). It is true that many patients can resume insulin treatment after interruption without untoward effects, but among the total number of persons with generalized insulin allergy, those with lapse in treatment constitute a high percentage. Perhaps, therefore, skin tests or other immunologic studies should be made in every patient who must be placed on insulin therapy for a second time. Also, the possibility of sensitization should be considered in the temporary insulin treatment of non-diabetic patients.

During the first course of treatment the development of insulin allergy seems to be characterized by a latent period. This lasted from 7 to 25 days in the case reports from the literature. This interval indicates the time necessary for the development of sensitization, and it shows also that it is valueless to perform skin tests as a routine procedure in any diabetic patient before beginning insulin therapy for the first time. The allergic predisposition apparently needs a period of sensitization for its activation. Skin tests need be made only when allergic symptoms appear. It may be useful to refer here to two complications of the insulin skin tests which we have observed *a*), insulin hypoglycemia and *b*), delayed reactions. Hypoglycemia can be anticipated and so prevented if many tests with insulin are made simultaneously. Delayed allergic reactions, usually generalized and severe, are likely to occur in patients with severe clinical symptoms. It has been stated that they can be avoided if epinephrin is given after the immediate reaction has been read. The patient should be warned of the possibility of this reaction and sometimes it may be better to perform the passive transfer test first. If this test is positive, skin tests may not be necessary. A negative passive transfer test, however, does not seem to exclude insulin allergy.

Allergic history. A history of any allergy should suggest the possibility of allergy to insulin. The majority of diabetic patients with asthma, hay fever and other allergic conditions, however, are able to undergo insulin treatment without any complication

[2] After this paper was completed, Philip Wasserman and I. Arthur Mirsky's paper on "Immunologic identity of insulin from various species" appeared in *Endocrinology* 31: 115. 1942. These authors demonstrated conclusively the immunological identity of insulin derived from beef, pork, sheep, bison, dog, and man.

although mild local reactions are not uncommon. Skin tests will help to rule out general insulin allergy and to find the least irritating preparation, which will be crystalline insulin in most instances.

Eosinophilia is of little significance in insulin allergy as well as in allergy in general. Patients with insulin allergy do not differ from non-allergic patients in whom no or only a slight eosinophilia has been found in response to insulin injections (4, 13). Moreover, a pre-existent eosinophilia does not indicate danger of insulin allergy.

Insulin allergy and insulin insensitivity. In one of our patients insulin allergy preceded the development of severe insulin resistance (*case 7*). Two other patients were allergic and insensitive at the same time. The insensitivity was established with the Himsworth test (11). Similar observations have been reported in the literature (4) and it has been suggested that both conditions may have the same cause. But, as Harten and Walzer state, 'insulin refractoriness is by no means a constant accompaniment of insulin allergy' (5). The majority of patients with allergic symptoms showed no change in their hypoglycemic response to insulin (5, 6) and, on the other hand, patients with insulin resistance offer allergic symptoms only occasionally (14). In general, both conditions seem to be independent of each other in their symptomatology as well as in the mechanism which causes them.

Therapy. Intramuscular administration of insulin, treatment with calcium, histamine, histaminase (15) and epinephrin have been recommended, as well as specific desensitization. The desensitization is performed either by giving multiple graduated doses of insulin at short intervals over a period of several hours, or by giving a very small insulin dose a short time before the therapeutic dose is injected. Good results have been reported in patients with localized allergic reactions. These procedures, however, are not always successful in the presence of generalized insulin allergy. In 6 cases of our series and in 11 of the 15 cases from the literature, the treatment had to be discontinued because of persistence or recurrence of allergic symptoms. Under these circumstances it is a rather fortunate coincidence that the diabetes in most of these patients is of only moderate severity, and with some effort can be controlled by diet alone.

SUMMARY

In contradistinction to the rather frequent, mild and transient local allergic reactions after insulin, which mostly are not due to insulin itself but to unspecific substances present in the insulin preparation, generalized insulin allergy is a rare but severe complication in the treatment of diabetes. Observations and immunologic studies on 8 of our cases and 15 from the literature indicate that this condition occurs predominantly in patients of the middle or high-age group with moderately severe diabetes. Interrupted insulin treatment seems to predispose to allergy. Skin tests may be advisable in all patients who resume insulin treatment, and in those who have clinical symptoms suggestive of insulin allergy.

CASE REPORTS

Case 1 gives the history of a patient who developed generalized insulin allergy during the first course of treatment and who was insulin sensitive.

Case 1, L.H., (*169 663*), a female, was 63 years old when diabetes was first diagnosed. For 5 years she followed a diet only, but was never free of polydypsia and polyuria. In 1937, at the age of 68 she came to Billings Hospital because of a lump in the left breast which had developed a few months before hospitalization and because of diabetic symptoms. The tumor was found to be a carcinoma and mastectomy was performed after the diabetes had been brought under control by diet (C 100, P 60, F 150) and 20 U of regular insulin. The postoperative course was uneventful. However, 2 weeks after the insulin treatment had been started the patient began to complain of itching and painful swelling at the site of the injections. These local reactions increased in severity and duration and would reach 'the size of a man's hand.' They became indurated and persisted up to 24 hours. Soon, general symptoms developed. The face became swollen, the eyelids appeared puffy, urticaria was present at various parts of the body and the patient complained of headaches, nausea and vomiting. Skin-tests were made at that time and were positive with various brands of commercial insulin. The patient gave no history of allergic reactions previous to insulin treatment and there was no history of allergy in her family. It was decided to stop the insulin injections and to attempt diabetic control with diet alone. The local reactions disappeared immediately, the general symptoms gradually. The diabetes was controlled on diet for about one year, after which time it became worse. The fasting blood sugar reached 263 mg. per cent and severe glycosuria recurred. A new series of insulin skin tests was positive. Since crystalline insulin gave the mildest reaction, the patient was advised to use 10-0-10 U of this preparation daily. Within a few days the diabetes was under control again, but the previous local and generalized reactions reappeared to an even more severe degree. Therefore intradermal desensitization with minute amounts of crystalline insulin at short intervals was attempted. On the first day a total of 12.4 U was given over a period of 15 consecutive hours at intervals of 30 minutes. The first dose was 0.001 U in 0.1 cc. volume. The doses were increased progressively to a final dose of 1.0 U in 0.25 cc. Only very mild local reactions were noted during this time. On the second day a first dose of 0.1 U was given intradermally, which was followed by subcutaneous injections of 1.0 unit each at hourly intervals. During the following days it became possible to increase the single doses and to decrease the number of injections. Finally, 12 U could be given twice daily and were sufficient for the diabetic control. But,

again, 2 weeks later local and generalized reactions recurred. Gastro-intestinal symptoms with nausea and vomiting and generalized urticaria made it necessary to stop the insulin treatment. The patient tried to manage on diet alone but was not successful. Ten months later, she developed bronchopneumonia and diabetic acidosis. Because of the previous experiences the family physician did not give insulin. When she entered the hospital she was in deep coma; insulin was given immediately, but the patient died a short time after admission. The autopsy (Dr. Paul Cannon) revealed lobar pneumonia in the left upper lobe, edema and hypostatic bronchopneumonia in the other lobes. The pancreas showed considerable acinar atrophy and fatty infiltration with marked hyalinization and interstitial fibrosis in the islets of Langerhans. The liver showed fatty infiltration. No significant changes were found in other organs.

Cases 2 and 3 developed generalized insulin allergy after lapse of treatment. *Case 2* did not have any allergic symptoms during the first course of treatment, whereas *case 3* had already shown local reactions when he received insulin in the first period.

Case 2, *R.A.*, (*193 284*), a 63-year-old white housewife had been a diabetic patient for about 6 years before she came under our observation in 1938. She was never seriously sick and did not have any symptoms of allergic diseases. However, one of her sons had hay fever. When diabetes was first diagnosed, she was placed on a diet and 20 U of regular insulin. The insulin treatment was discontinued after a few weeks, but it was resumed several times for short periods during the following 3 years. When she was seen in our clinic, the diabetes was under good control on diet alone. However, one year later in the spring of 1940, it seemed advisable to give insulin. The patient was instructed to take 10 U of protamine zinc insulin. Within a week the mild glycosuria, polyuria and general weakness disappeared. On the ninth day of treatment local reactions began to develop which became worse from day to day. At first, swelling, redness and itching were localized at the site of injection and disappeared after several hours. Later the urticaria spread over the body and persisted for more than 24 hours. On the twelfth day she came to the clinic and presented generalized urticaria with the most severe involvement on the inner surfaces of elbows and knees. The lips were swollen and the patient complained of severe headache, joint pain, nausea and vomiting. At that time a passive transfer test was performed which was positive. Insulin was discontinued and the reactions disappeared slowly. Insulin skin tests were performed a week later. They were positive with all tested preparations. The reactions to these tests were severe and persisted for almost 3 days. An attempt at desensitization was unsuccessful because of severe local reactions during this procedure. Intramuscular injections of insulin alleviated the reactions slightly, but the patient insisted on discontinuation of insulin treatment. This was possible after further restriction of the diet. Skin tests in the spring of 1942 gave the same results as the previous tests.

Case 3, *W.B.*, (*253 200*), was a 51-year-old white man with a diabetic history of 12 years' duration. About 10 years ago insulin treatment was begun but soon discontinued because of local reactions which had appeared after the very first injection. When he came to our Clinic in 1939 he complained of general weakness, polydypsia and polyuria; the fasting blood sugar was 179 mg. per cent and more than 50 gm. of glucose was excreted in the urine during 24 hours. Dietary restriction (C 100, P 75, F 150) was not sufficient to control the diabetes and the patient was advised to take 15 U of protamine zinc insulin. He did so for 10 days and the hyperglycemia as well as the glycosuria improved. But the same reactions recurred which were present 10 years previously. Swelling, redness and itching at the site of injection increased from day to day. After 10 days these reactions became generalized and involved both thighs and legs, shoulders and arms. Knee and elbow joints were swollen and very painful. These reactions persisted for more than 24 hours and were accompanied by headache and slight fever. The patient did not have a history of any other allergic disease, nor were allergic diseases known in his family. The passive transfer test and the insulin skin tests were positive. The skin tests were followed by generalized urticaria and malaise. Similar reactions occurred when insulin was given intramuscularly and when a desensitization was attempted with an intradermal injection of a minute dose of insulin followed by the therapeutic dose subcutaneously. The diabetes was controlled finally by restricted diet alone.

Case 7 represents a condition in which insulin allergy preceded the development of insulin resistance. The complete history of this case will be published separately.

Case 7, *H.L.*, (*33 205*), a 52-year-old man, came under our observation in December, 1938. As early as 1925 he was told that there was sugar present in the urine. In the following years he developed retinitis, bilateral cataract and arteriosclerotic heart disease. The diabetes did not receive attention, however, until he came to Billings Hospital because of bronchopneumonia and cardiac failure. At that time the fasting blood sugar was normal, but the urine contained sugar. A glucose tolerance test confirmed the diagnosis of diabetes mellitus and the patient was placed on a restricted diet (C 100, P 70, F 150). About 6 months later he began to notice increasing polydypsia and polyuria, neuritic pain in legs and arms, general weakness and weight loss; the fasting blood sugar was found to be 286 mg. per cent and the sugar excretion about 10 gm. in a 24-hour urine specimen. He was hospitalized and insulin treatment was started. A total of 50 U (30 U of protamine zinc plus 20 U of regular insulin) was necessary to keep the blood sugar within normal limits and the urine sugar free. From the seventh day on, the sites of injection became swollen, red and indurated, itched and were painful for 24 to 48 hours. The appearance of these reactions did not vary with variation of the site of injection (thigh, arm or abdominal wall) or with the type of insulin used (regular, crystalline or protamine zinc insulin). A series of insulin skin tests was performed. All tests were positive. Intramuscular application of insulin was tried and it was found that no or only little local reactions occurred. Therefore this mode of injection was used in the further treat-

ment. The diabetes remained under control on the previous diet and 50 U of insulin daily until 7 months later, when without apparent reason the glycosuria increased. Daily doses of 100 to 200 U of insulin were insufficient for diabetic control and in July, 1940, the patient was hospitalized because of diabetic acidosis. Since massive doses of insulin (1000 U within 24 hours) had very little effect, insulin was given intravenously. After two injections of 100 units each at an interval of one hour general urticaria developed with severe involvement of all sites of previous insulin application. Intramuscular injections were resumed and finally the diabetic acidosis came under control. The passive transfer test with the blood of this patient was positive and the insulin precipitation test was strongly positive. The blood, however, did not inhibit the insulin hypoglycemia in rabbits. Following this acidosis and general allergic reaction, the patient required about 500 to 1000 U of insulin daily, but no satisfactory control of the diabetes could be achieved. An attempt at biological desensitization with the method of Karr and associates (12) was unsuccessful. The patient died 6 months later.

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Present Status of the Use of Male Sex Hormones and Chorionic Gonadotropins as Growth Stimulating Factors

[Endocrines and Growth]

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THE VALUE of chorionic gonadotropin as a therapeutic agent in hypogenitalism and cryptorchidism, and of the testosterone compounds in eunuchoids and castrates, has been well established. Coincident with the improvement in the genital development of boys under chorionic gonadotropin therapy, an increase in the growth rate beyond the expected average was observed by Lurie and Hertzman (1), Dorff (2), Thompson (3), and by us.

Rubinstein and Solomon (4–7) demonstrated an increase in body length of white rats following the administration of moderate doses of testosterone compounds. Webster and Hoskins (8) Rapfogel (9), Albright et al. (10), Brown and Ross (11) and Goldzieher (12) used testosterone propionate in children presenting growth deficiency and observed an increase in growth rate in these children and a few adolescents. There are several contradictory reports pertaining to the effect of various hormones on bone growth, bone density and epiphyseal union in rats, mice and guinea pigs. Silberberg (13) showed that after a temporary acceleration, there is a retardation of bone growth. Turner, et al. (14) did not find a difference in the skeletal development between infantile rats treated with testosterone and the controls. McCullagh and McGurl (15) reported an increase in the rate of epiphyseal union in some of their patients treated with testosterone.

CLINICAL DATA

Of a group of 82 children who received chorionic gonadotropin therapy for various indications such as certain types of cryptorchidism, hypogenitalism, adiposogenital dystrophy and growth deficiency, observations were made on growth in 50 cases and the data are reported.

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Of another group of 49 children and adolescents receiving various forms of hormonal therapy for primary growth retardation, 15 received testosterone propionate and observations on growth were made. Thus, the total number of cases presented consists of 65 children and adolescents. Each group is analyzed in detail in tables 1 and 2.

Chorionic gonadotropin[1] was administered arbitrarily in the following manner: 100 to 750 I.U. two to three times a week parenterally for periods from 2 months to 2 years, with varying intervals of rest, (table 1).

Testosterone propionate[2] therapy was administered arbitrarily in the following manner: 10 to 25 mg. parenterally twice a week for periods from 3 to 6 months (table 2).

In all cases treated primarily for growth deficiency, and in the majority of cases treated for hypogenitalism and cryptorchidism, roentgen-ray studies were made of the skull and long bones at intervals throughout the course of therapy and subsequently. Other laboratory studies included determination of the B.M.R., Wassermann reaction, blood sugar, cholesterol, calcium, phosphorus and phosphatase, complete blood studies and routine urinalysis.

The data for each patient were tabulated in the group in which they fell at the time of the first visit. At the last visit, before the final computation of the data in this paper, the height was measured and tabulated. Any change in grouping was estimated and recorded; an estimate of the average of increase, the *status quo* and the decrease in growth rate was made in each case.

[1] Chorionic gonadotropin (A.P.L.) and anterior pituitary extract (Growth Complex) were supplied through the courtesy of Ayerst, McKenna and Harrison, Montreal, Quebec and Rouses Point, N. Y.

[2] Testosterone propionate (Oreton) was supplied through the courtesy of Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J.

TABLE 1. EFFECT OF CHORIONIC GONADOTROPIN ON GROWTH

Case	Age	Chief Complaint	Duration of Therapy	Total Amount	Initial Ht. and Date	Ht. and Date at End of Therapy	Growth Increase	Latest Ht. and Date	Growth after Cessation of Therapy	Progress in Burgess Grouping[1]
1, *DF*	yr. 14	Growth retardation	mo. 13	I.U. 26,000	in. 9/27/34 46.75	in. 10/12/35 51.25	in. 4.50	in. 10/30/37 57.00	in. 5.75	% +1
2. *SM*	6.5	Cryptorchidism	10	34,500	8/ 3/35 47.00	11/21/36 48.50	1.50	9/21/40 56.75	8.2	0
3, *JS*	8	Cryptorchidism	3	8,000	2/19/35 47.50	8/12/35 49.75	2.25	*		+30
4, *IK*	5.5	Cryptorchidism	3.5	4,200	3/ 1/36 44.25	3/ 1/37 46.75	2.50	3/25/42 59.00	12.25	+30
5, *EM*	6	Cryptorchidism	4	17,000	6/ 8/36 49.75	2/18/38 53.50	3.75	6/17/42 61.75	8.25	0
6, *RO*	15	Adiposogenital dystrophy	3	18,000	9/12/36 61.00	3/27/37 63.00	2.00	2/19/38 65.25	2.25	+2
7, *IS*	4	Cryptorchidism	24	131,200	2/11/36 44.00	2/18/39 51.50	7.50	5/ 2/42 56.00	4.50	+10
8, *HS*	12	Cryptorchidism	3	45,000	11/24/36 55.75	3/ 4/37 56.50	0.75	11/26/38 59.00	2.50	−10
9, *AS*	6	Cryptorchidism	2	10,000	9/22/36 45.00	11/21/36 48.50	3.50	*		+43
10. *JC*	10	Cryptorchidism	16	53,500	6/ 8/37 53.00	10/29/38 55.75	2.75	12/ 3/38 56.75	1.00	+20
11, *LD*	8	Cryptorchidism	5	25,000	10/16/37 49.00	9/24/38 49.00	0.00	6/13/42 60.25	11.25	−20
12, *RL*	3.5	Cryptorchidism dystrophy	23	93,500	10/30/37 35.00	1/11/41 50.00	15.00	5/16/42 54.50	4.50	+79
13, *HS*	11	Hypogenitalism	4	24,000	5/ 1/37 54.50	3/28/39 56.50	2.00	2/ 6/40 58.50	2.00	−25
14, *EW*	7	Hypogenitalism	6	36,000	9/11/37 47.75	3/25/40 53.00	5.25	2/28/42 57.00	4.00	+20
15, *MF*	11	Cryptorchidism	3	15,000	12/24/38 53.50	3/24/39 53.50	0.00	6/ 6/42 61.00	7.50	0
16, *SG*	1	Cryptorchidism	4	20,000	12/ 2/38 32.75	4/ 4/39 35.00	2.25	6/27/41 40.50	5.50	+48
17, *EM*	11	Cryptorchidism	3.5	17,000	10/29/38 53.00	2/ 4/39 53.50	0.50	9/28/40 57.25	3.75	+10
18, *HN*	7	Cryptorchidism	2	9,000	10/29/38 50.00	2/18/39 51.00	1.00	9/21/40 55.00	4.00	+7
19, *HN*	10	Growth retardation	14	84,000	8/23/38 49.00	6/ 1/40 52.75	3.75	2/14/42 59.00	6.25	+26
20, *JW*	18	Hypogenitalism	2	8,000	3/29/38 61.00	11/ 1/38 63.75	2.75	4/ 7/42 66.25	2.50	+30
21, *LA*	8	Cryptorchidism	2	17,000	3/ 7/39 43.50	6/22/39 49.00	5.50	10/19/40 51.50	2.50	+50
22, *MA*	7.5	Adiposogenital dystrophy	5	22,000	6/11/39 54.00	11/27/39 56.25	2.25	4/23/38 57.50	1.25	0
23, *HD*	7	Cryptorchidism	2	6,000	5/ 6/39 45.25	7/10/39 45.75	0.50	11/23/40 48.50	2.75	0

TABLE 1 (*Cont'd.*)

Case	Age	Chief Complaint	Duration of Therapy	Total Amount	Initial Ht. and Date	Ht. and Date at End of Therapy	Growth Increase	Latest Ht. and Date	Growth after Cessation of Therapy	Progress in Burgess Grouping[1]
	yr.		mo.	I.U.	in.	in.	in.	in.	in.	%
24. *JC*	10	Hypogenitalism	4	22,000	11/ 4/39 54.50	9/21/40 56.25	1.75	2/14/42 58.75	2.50	0
25. *RF*	5	Cryptorchidism	11	40,000	10/28/39 43.50	9/21/40 45.00	1.50	*		+20
26. *WH*	10	Cryptorchidism	8	32,000	8/31/39 52.25	10/19/40 54.50	2.25	*		0
27. *RS*	12	Cryptorchidism	3	24,000	9/12/39 52.75	6/20/40 54.25	1.50	6/13/42 59.25	5.00	+4
28. *DS*	12	Cryptorchidism	5	30,000	12/29/39 60.50	3/ 1/41 63.75	3.25	6/ 6/42 68.75	5.00	+4
29. *NZ*	4	Hypogenitalism	6	14,400	1/ 3/39 42.25	7/11/39 44.75	2.50	*		+13
30. *DC*	8	Adiposogenital dystrophy	10	40,000	1/ 3/39 55.75	1/ 3/40 57.25	1.50	6/ 1/42 60.50	3.25	0
31. *RB*	7	Cryptorchidism	10	29,500	11/16/40 47.50	11/ 8/41 51.50	4.00	5/ 9/42 52.25	0.75	+40
32. *MB*	16.5	Growth retardation	3	8,000	10/19/40 55.50	3/22/41 56.25	0.75	5/ 9/42 60.25	4.00	+5
33. *SG*	5	Cryptorchidism	4.5	27,000	9/ 9/40 43.50	2/ 8/41 44.00	0.50	12/20/41 47.00	3.00	+15
34. *SH*	18	Growth retardation	3	9,000	9/ 7/40 56.75	12/14/40 57.00	0.25	7/ 1/41 57.00	0	0
35. *DL*	5.5	Hypogenitalism	6	10,450	10/17/40 48.50	4/27/41 50.00	1.50	*		0
36. *BR*	11	Cryptorchidism	2	15,000	1/11/40 57.00	8/ 5/41 60.25	3.25	12/30/41 61.00	0.75	0
37. *JS*	5	Cryptorchidism	5	14,250	3/21/40 43.00	3/ 1/41 46.00	3.00	4/25/42 49.25	3.25	+10
38. *RD*	15.5	Growth retardation	4	16,000	5/29/41 59.00	10/ 4/41 60.75	1.75	5/23/42 61.00	0.25	0
39. *WD*	7	Cryptorchidism	3	18,000	11/15/41 58.00	3/21/42 59.75	1.75	5/23/42 60.25	0.50	+2
40. *RJ*	11	Cryptorchidism	5	22,000	12/20/41 53.25	5/16/42 55.25	2.00	6/16/42 55.50	0.25	+15
41. *MN*	7	Growth retardation	5	9,000	11/15/41 45.00	4/25/42 46.25	1.25	6/ 9/42 46.75	0.50	0
42. *SS*	16	Hypogenitalism	6	24,000	3/ 1/41 62.75	9/16/41 63.75	1.00	5/16/42 64.75	1.00	+11
43. *WS*	11	Hypogenitalism	3	16,000	4/19/41 57.00	7/12/41 57.50	0.50	8/14/41 58.50	1.00	+6
44. *WS*	7.5	Cryptorchidism	4	4,000	3/15/41 50.75	7/16/41 52.00	1.25	4/ 9/42 53.25	1.25	+3
45. *WS*	9	Hypogenitalism	3.5	13,000	7/17/41 53.50	11/29/41 54.25	0.75	*		0
46. *AT*	9	Adiposogenital dystrophy	5	25,000	12/13/41 58.75	5/11/42 60.00	1.25	*		−3

TABLE 1 (*Cont'd.*)

Case	Age	Chief Complaint	Duration of Therapy	Total Amount	Initial Ht. and Date	Ht. and Date at End of Therapy	Growth Increase	Latest Ht. and Date	Growth after Cessation of Therapy	Progress in Burgess Grouping[1]
	yr.		mo.	I.U.	in.	in.	in.	in.	in.	%
47, *JC*	11	Growth retardation	2	12,000	3/ 7/42 48.75	5/23/42 49.25	0.50	**		+5
48, *MC*	14	Growth retardation	2	12,000	3/ 7/42 53.75	5/23/42 54.25	0.50	**		+2
49, *LG*	11	Cryptorchidism	4	20,000	1/17/42 55.00	5/16/42 56.00	1.00	6/16/42 56.25	0.25	0
50, *RH*	9.5	Cryptorchidism	3	21,500	1/20/42 56.50	4/10/42 58.00	1.50	*		+4

[1] The difference between the initial and final grouping constitutes the percentage of improvement or retardation for each individual child.
* Did not report for final check-up.
** Therapy discontinued recently.

CLINICAL OBSERVATIONS

The administration of chorionic gonadotropin and testosterone propionate was followed in most instances by an acceleration of the growth rate as compared with the Burgess chart standards. In addition to the improvement in stature, other effects observed were development of secondary sex characteristics and improvement in general vitality, mental alertness and social attitude. In the instances in which development of external genitalia preceded the improvement in height therapy was discontinued either temporarily or permanently.

FIG. 1. A. *Case 12* (table 1). *R. F. L.*, age 3.5 years; height, 35 in.; Oct. 30, 1937. *B.* Patient, age 4 years and 2 mo.; height, 41.5 in.; June 28, 1938. *C.* Patient, age 7 years and 8 mo.; height 4 ft., 5½ in.; Dec. 6, 1941. Chorionic gonadotropin therapy. See case reports.

In the group of children who showed improvement under chorionic gonadotropin therapy the percentage of improvement ranged between 1 and 79 per cent as estimated from the Burgess charts, the average improvement being 18.2 per cent. In the group of children treated with testosterone propionate the percentage of improvement ranged from 2 to 30 per cent, the average being 10.9 per cent. Two cases receiving chorionic gonadotropin and one receiving testosterone propionate are reported.

CASE REPORTS

Case 12 (table 1), *R.F.L.*, was first seen in the Endocrine Clinic Oct. 30, 1937, at the age of 3.5 years because of genital and mental retardation and a speech defect consisting of stuttering and indistinct enunciation. At the time of admission the height was 35 inches and the weight 38 lb. (fig. 1, *a*). There was a retardation in the genital development; the penis was very small, scrotum was contracted and empty, small pea-size testes were located at the external ring. Roentgenograms of the long bones did not reveal any abnormalities of bone development. The sella turcica was somewhat small for the age.

The child was placed on chorionic gonadotropin therapy 500 I.U. two to three times per week. On June 28, 1938, the height was 41.5 inches, an increase of 6 inches in a period of 8 months. The general status had improved; he became alert, his speech was cleared, and he displayed an interest in people and his surroundings. The genitalia (fig. 1, *b*) showed a marked increase in size; both testes were normal size, the left was in the lower, and the right in the upper part of the scrotum. Treatment was continued with intervals of rest, and roentgen-ray examination of the wrists and hands in 1939 showed an advance in

TABLE 2. EFFECT OF TESTOSTERONE PROPIONATE ON GROWTH

Case	Age	Chief Complaint	Duration of Therapy	Total Amount	Initial Ht. and Date	Ht. and Date at End of Therapy	Growth Increase	Latest Ht. and Date	Growth after Cessation of Therapy	Progress in Burgess Grouping[1]
	yr.		mo.	mg.	in.	in.	in.	in.	in.	%
1, *EB*	13	Growth retardation	6	1,200	8/10/41 55.00	2/18/42 58.00	3.00	*		+8
2, *MB*	17	Growth retardation	6	1,200	7/ 8/41 57.50	1/21/42 60.00	2.50	5/ 9/42 60.25	0.25	+5
3, *JC*	10.5	Growth retardation	4	800	9/16/41 47.25	1/10/42 47.75	0.50	5/23/42 49.25	1.50	+5
4, *MC*	13	Growth retardation	2	300	12/ 7/41 53.25	2/10/42 53.50	0.25	5/23/42 54.25	0.75	+2
5, *JC*	12	Cryptorchidism	2	110	12/ 3/38 56.75	4/29/38 57.00	0.25	12/ 6/41 64.50	7.50	+20
6, *HC*	8	Growth retardation	4	300	9/ 1/42 47.25	1/31/42 49.25	2.00	3/20/42 50.25	1.00	+25
7, *CW*	11	Growth retardation	3	500	7/22/41 55.00	11/22/41 56.50	1.50	2/28/42 57.00	0.50	+20
8, *AF*	14	Growth retardation	2.5	500	6/14/41 57.50	10/18/41 58.00	0.50	5/ 9/42 60.50	2.50	+5
9, *LK*	10	Growth retardation	4	320	7/10/41 45.50	11/15/41 47.00	1.50	6/ 6/42 48.25	1.25	+3
10, *RR*	14	Growth retardation	3	575	5/10/41 57.25	11/29/41 59.00	1.75	6/ 6/42 60.50	1.50	+5
11, *SS*	16.5	Growth retardation and hypogenitalism	4	800	9/16/41 63.75	1/10/42 64.50	0.75	5/16/42 64.75	0.25	+11
12, *WS*	15	Growth retardation	4	690	6/14/41 57.50	2/28/42 60.00	2.50	5/ 9/42 60.75	0.75	+11
13, *NW*	11.5	Hypogenitalism	2	160	3/17/40 63.00	5/27/40 63.75	0.75	6/20/42 66.75	3.00	−3
14, *RD*	16	Growth retardation	6	200	10/ 4/41 60.75	5/ 8/42 61.00	0.25	**		0
15, *JW*	18	Hypogenitalism and growth retardation	36	1,440	11/ 1/38 63.75	1/ 6/41 65.75	2.00	4/ 7/42 66.25	0.50	+11

[1] See footnote to table 1. * Did not return for final check-up. ** Therapy recently discontinued.

development beyond his chronological age. Hormonal therapy was, therefore, discontinued and instructions were given concerning nutritional and vitamin requirements. When seen again on May 7, 1940, he was 48.5 inches in height and weighed 48.25 lb. Since some regression in the genitalia had occurred, therapy was resumed and continued for a period of 4 months after which time it was again discontinued because of a favorable and sufficient response. On Dec. 6, 1941, he was 53.5 inches tall and weighed 60 lb. The genital development (fig. 1, *c*) was normal, but roentgenograms of the wrists and hands still showed the bone age to be in advance of the chronological age. The growth rate continued to be accelerated, however, as noted in the accompanying growth chart (fig. 2).

Case 18 (table 1), *H.N.*, was admitted to the Endocrine Clinic on July 19, 1937, at the age of 9.5 years. The boy was brought to the clinic by a guardian from the corrective institution to which he had been committed for repeated offenses, such as theft and arson. He and a group of boys of whom he seemed to be the leader, had started about 12 neighborhood fires. It occurred to the Judge, noting the child's stunted growth, that these criminal tendencies may have resulted from the child's resentment of his stature, and if this could be corrected, the child might overcome his anti-social attitude.

At the time of admission the height was 46.75 inches and weight 50.5 lb. Physical examination revealed short stature and normal genitalia; the facial expression was

stubborn and resentful (fig. 3,*a*). Roentgen-ray examination of the sella turcica and long bones did not show any abnormality in bone development.

Therapy with anterior pituitary growth extracts[1] was initiated on Aug. 19, 1937, 1 to 2 cc. being administered parenterally 2 to 3 times per week. This therapy was continued with intervals of rest of one month every 2 to 3

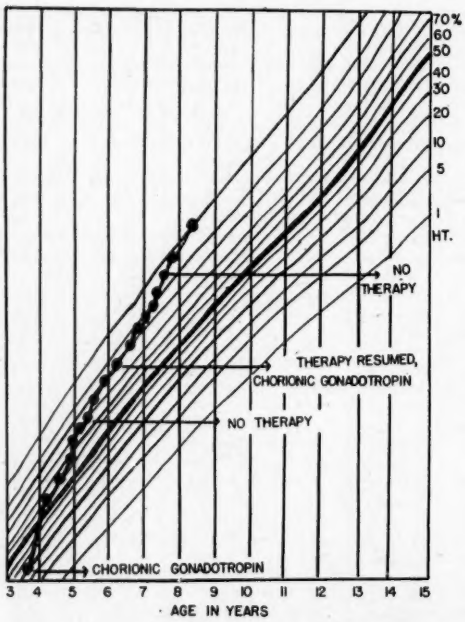

FIG. 2. Growth chart of *case 12* (table 1), from 3.5 to 8.5 years of age.

months until November, 1938, at which time the height was 49 inches and the weight 57 lb. Although this was an increase of 2.25 inches in 15 months, there was no increase in the growth rate. Since the boy's growth was of primary interest, therapy was changed to chorionic gonadotropin, because satisfactory results had been obtained in other cases. This therapy, with irregular periods of rest was maintained until May 19, 1939, at which time the height was 49.75 inches and the weight 57.5 lb.

There was a marked development of the genitalia (fig. 3, *b*). The boy's behavior improved so that he was paroled in the custody of foster parents, the atmosphere of his own home being considered unsuitable at that time.

After an interruption of 3 months in treatment, therapy was resumed and continued until Oct. 25, 1940, at which time the height was 54 inches and weight 73.5 lb. Thus, in 3 years he grew 7.25 inches.

Roentgen-ray examinations of the hands and wrists on May 9, 1939, and Oct. 25, 1940, did not reveal any significant changes. The bony development was in harmony with the advancing chronological age. Therapy was then discontinued and the child was not seen again until May 15, 1941, at which time the height was 56.5 inches, an increase of 2.5 inches in 7 months following cessation of therapy. The boy's physical and genital development showed normal progress (fig. 3, *c*).

When last seen, Feb. 12, 1942, the height was 59 inches, an increase of 5 inches over a period of 16 months following cessation of therapy and a total increase of 12.25 inches over a period of 4 years and 7 months. Roentgen-ray examination of the hands and wrists when the boy was last seen at the age of 14, revealed the osseous and epiphyseal development to be normal for his age. As far as the behavior problem is concerned, the boy continued to improve steadily, and has been paroled in the custody of his parents for the last 2 years.

Case 2 (table 2), *M.B.*, was first seen on Aug. 2, 1940, in the Endocrine Clinic for stunted growth at the age of 16. The height was 54.75 inches and the weight was 76.75 lb. Physical examination (fig. 4, *a*) showed the boy to be of short stature with a childish facial expression, no pubic hair, and with small penis, scrotum and testes, although the latter were in normal position. Roentgen-ray examination of the hands and wrists on Aug. 15, 1940, revealed a retardation of bone growth and delay in epiphyseal union.

Therapy with anterior pituitary growth extract was initiated on Aug. 15, 1940, and on Nov. 23, 1940, chorionic gonadotropin was added, because there was no demonstrable increase in growth rate. The hormones were administered simultaneously, but in separate syringes. This therapy was continued with brief periods of rest until

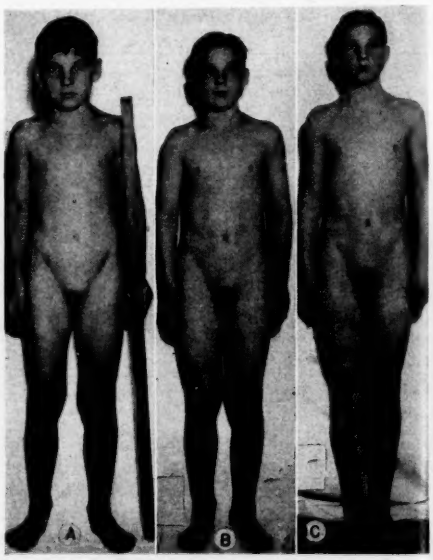

FIG. 3. *A. Case 18* (table 1). *H. N.*, age 9.5 years; height 46.75 in.; July 19, 1937. *B.* Patient, age 11 years, 4 mo.; height 49.75 in., May 9, 1939. *C.* Patient, age 13 years and 4 mo.; height, 4 ft. 8.5 in.; May 15, 1941. Chorionic gonadotropin therapy. See case reports.

July 8, 1941, at which time the height was 57.5 inches and the weight was 93 lb. Physical examination revealed marked maturation of the facial expression, an increased development of the chest and arms, and development of

external genitalia (fig. 4, *b*). Roentgenograms made on July 9, 1941, revealed no change from the findings of the previous examination. On July 10, therapy with testosterone propionate was initiated, 25 mg. being administered twice a week. This form of therapy was given for the purpose of increasing the rate of growth, and was continued until Nov. 15, 1941, at which time the height was 59 inches and the weight was 105.5 lb. While receiving therapy with growth hormones and chorionic gonadotropin this patient grew 3 inches in 13 months; a growth of 1.5 inches in 4 months was noted during testosterone propionate therapy. Roentgen-ray examination on Dec. 6, 1941, still showed a delay in bony development. Therapy with testosterone propionate was resumed on Jan. 31, 1942, at which time the height was 59.5 inches and the weight was 105.25 lb. Testosterone therapy was discontinued one month later and on May 16, 1942, the height was 60.25 inches, the weight 107 lb. Physical examination revealed further progress in muscular development, maturation of the facial expression and development of the genitalia and pubic hair (fig. 4, *c*). Roentgenograms of the hands and wrists on March 7, 1942, showed the same relative retardation in bone development as was seen before therapy was initiated.

DISCUSSION

Administration of chorionic gonadotropin for hypogenitalism, cryptorchidism and adiposogenital dystrophy is a generally accepted form of therapy, and has been employed by us for the last 8 years. While treating hypogenitalism and cryptorchidism with chorionic gonadotropin we were impressed by the growth stimulating potentialities of this form of therapy. Observations were made on 50 children who received chorionic gonadotropin and it was noted that the best growth response occurred in those patients who presented mainly symptoms of hypogenitalism and cryptorchidism. In those patients who presented symptoms of growth retardation chiefly, the chorionic gonadotropin was moderately effective. Of this group 62 per cent (31 children) showed an increase in the rate of growth; 30 per cent (15 children) maintained the original rate of growth and 8 per cent (4 children) were below the original rate of growth. No abnormal findings were noted except in 2 patients in whom there occurred a stimulation of bone growth and development beyond the chronological age.

The use of testosterone as a growth stimulating factor in children is a recent approach to the problem of growth and has been used by us for one year, although its value in the treatment of eunuchs and eunuchoids has been known for some time. Kochakian (16) and Kenyon et al. (17, 18) have demonstrated that the administration of testosterone compounds to experimental animals causes nitrogen retention which is essential for muscular and skeletal growth.

Because of the suggested possibility of early bone maturation, roentgenograms were made from time to time during and subsequent to periods of therapy and because of the effect of the testosterone compounds on the development of external genitalia in boys, the genitalia were frequently examined.

Fifteen children with growth retardation were

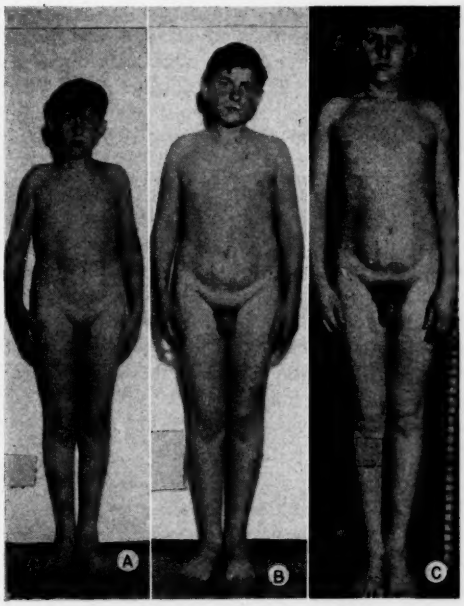

FIG. 4. *A. Case 2* (table 2). *M. B.*, age 16 years; height 4 ft., 6.75 in.; Aug. 2, 1940. *B.* Patient, age 17 years; height 4 ft., 9.5 in.; July 10, 1941. *C.* Patient, age 18 yr.; height 5 ft.; May 16, 1942. Testosterone propionate therapy. See case reports.

maintained under this form of therapy, and to date no harmful effects have been observed in these patients. When the genitalia showed a tendency to over-development therapy was discontinued. Of this group of 15 children, 13 showed an increase in the rate of growth, one maintained the original rate of growth and in one child the original rate of growth was lowered. Roentgen studies of the long bones were made at frequent intervals and at no time was there an indication of premature epiphyseal union. One year after the initiation of this therapy, the epiphyses remained open as noted at the time when treatment was begun; there was no marked change in bone density.

SUMMARY

Growth observations were made on 50 children treated with chorionic gonadotropin and on 15 children treated with testosterone compounds.

Chorionic gonadotropin was administered in doses of 100 to 750 I.U. two to three times a week for

periods ranging from 2 months to 2 years. Testosterone propionate was administered in doses of 10 to 25 mg. twice weekly for periods from 3 to 6 months.

Of the 50 children receiving chorionic gonadotropin 62 per cent (31 children) showed an advance in the growth rate; 30 per cent (15 children) maintained their expected growth rate; and 8 per cent (4 children) showed a decrease in the growth rate.

Of the 15 children treated with testosterone propionate 13 children showed an advance in the growth rate; one maintained the original growth rate; and one showed a lowering of the original growth rate.

No outstanding changes in the chemistry of the body processes and no demonstrable changes in bone structure were noted except in the 2 cases treated with chorionic gonadotropin in whom there was an advance in bone age. In all children whose growth rate fell below the accepted normal, there were no demonstrable roentgen-ray evidence to account for this occurrence. Stimulation in the development of secondary sex characteristics occurred but overstimulation was avoided by periodic interruptions in therapy.

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EDITORIALS

THE PARATHYROIDS AND PSYCHOSIS

In view of the intimate relationship between the parathyroid glands and calcium metabolism and of the influence of calcium upon the functions of the cells of the nervous system, it might be assumed that these glands would play an important rôle in clinical neurological and mental disturbances. In particular, hypoparathyroidism with its accompanying depression in the level of blood calcium might be expected to give rise, to, or to exaggerate, clinical disorders in which hyper-irritability is a notable feature. Whether, or to what extent, such is the case is not adequately known except as to the condition, tetania parathyropraevia.

In the older literature Timme described a syndrome in which the patients showed marked irrascibility, flying into ungovernable rage upon slight provocation and reacting with irrational violence. Under treatment with parathyroid extract, calcium and sunlight a marked improvement in the disposition was seen. Subsequently Shannon reported the cases of 8 children who developed convulsions followed by depression and irrational speech. As the condition progressed, night terrors, acute maniacal excitement with screaming, fighting and tearing of the clothes occurred. In 6 of the cases the condition was relieved by parathyroid extract.

Text books of psychiatry and of medicine lay little stress upon the relationship of parathyroid disorders to mental conditions, although for nearly a century it has been recognized that psychosis may develop during the course of clinical tetany. In a recent article Greene and Swanson* have reported that they had been able to find in the literature of the preceding 19 years only 4 cases in which psychosis appeared as a complication of tetany. Having themselves, however, noted 5 such cases in 18 patients with hypoparathyroidism observed in their own clinic, they surmised that the association is actually more frequent than is commonly recognized.

In their cases, as well as those reported in the earlier literature, the usual type of psychosis was a toxic delirium although other types, including dementia, have been noted. There is, however, apparently no specific type of psychosis which is actually characteristic of parathyroid deficiency. Among the nervous symptoms often seen in this condition are anxiety, depression, and a sense of impending disaster. When the condition reaches the severity of an actual psychosis, delusions and hallucinations appear. In 2 of the cases reported by Greene and Swanson the hallucinations were of a sexual type and in both instances the eroticism had been markedly augmented prior to the onset of the psychosis. Delusions of persecution occurred in 2 other cases and suicide was attempted in both instances.

According to the scanty evidence now available, it appears that if a psychosis does occur in the course of parathyroid tetany it develops within the first 3 or 4 months of that disorder although it may appear within a few days or may be delayed several weeks. The authors comment that psychic disturbances may be the first and only manifestation observed and that the etiology of the psychosis may be missed unless search is made for the characteristic signs of parathyroid deficiency. Frank carpopedal spasms and convulsions are usually absent from the picture.

The prognosis in this psychosis is usually good although the condition may persist for several months. Upon the institution of treatment for the glandular condition there is usually a delay in the mental improvement of from 1 to 4 weeks after the calcium level has been normalized and then another 3 or 4 weeks are required for complete recovery. Recovery having been attained, recurrence of the tetany is commonly not followed by a recurrence of psychic disturbances. Careful neurological examinations in the cases of Greene and Swanson failed to disclose any residual damage to the central nervous system. The facts that the psychosis is of rather early onset in the course of the tetany and that it does not recur with recrudescence of the parathyroid deficiency suggest to the authors that the psychosis may be due to failure of the brain to adjust promptly to the acute chemical changes to which it is subjected.

The marked discrepancy between the frequency of psychosis in tetany in the experience of the recent writers and the rare reports of the condition in other writings obviously suggests that more searching study might bear out Greene and Swanson's conjecture that the association of the two disorders is actually more frequent than is usually recognized. If parathyroid deficiency of the more marked grades actually does have the serious repercussions in the mental sphere that are suggested, the interesting question arises as to what part the parathyroids may play in the mood swings of everyday life. The problem might have some appeal to organically-minded psychologists.

R. G. H.

* Psychosis in hypoparathyroidism; with a report of five cases. Greene, J. A., and L. W. Swanson. *Ann. Int. Med.* 14: 1233. 1941.

RELATION OF THE THYROID GLAND TO BLADDER TONUS

Although several authors have reported atony of the bladder as of frequent occurrence in clinical hypothyroidism, the relationship has apparently not gained wide recognition. In a recent report Sherrill and MacKay[1] have called attention to their own experience of the association of the two conditions and have further reported an experimental study of the subject, under controlled conditions.

Three groups of adult male rats, of 8 individuals each were placed on a special adequate diet at the age of 170

[1] *J. Urol.* 46: 34, 1941.

days. A month later the members of one group were thyroidectomized, those of another group were given desiccated thyroid in their diet and the third group were kept as controls. Some three months following, the members of each group were tested for bladder tonus. Each was given an appropriate dose of a radio-opaque iodine compound, following which roentgen-ray photographs were made of the animals in the supine position to show the size of the bladder. The animals of the thyroidectomized group, in general, were found to have a greater bladder volume than did the normal group, whereas the thyroid-fed group showed a slightly smaller volume.

Subsequently a functional test of the tonus was made in each case by anesthetizing the animals, quickly filling the bladders by use of a 20-gauge hypodermic needle with normal NaCl solution raised to a pressure of 600 mm. of the fluid. The time required for the pressure to fall to 200 mm. was then recorded in seconds. The average for the control group was 2 seconds, the range being from 1 to 5 seconds. In the thyroidectomized group the emptying time was three times as long, averaging 6 seconds and ranging from 3 to 10 seconds. The results in the thyroid-fed group were not remarkable, averaging the same as in the controls.

As to the cause of the flaccidity of the bladder wall in the hypothyroid animals, the authors suggest that depression of nervous responsivity may have been somewhat of a factor, but that it was most likely due chiefly to the depression of metabolism of the muscular tissue of the bladder wall. R. G. H.

Abstracts of
CURRENT CLINICAL LITERATURE

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GONADS

ARNELL, R. E., AND WM. F. GUERRIERO.

Nutritional edema in pregnancy with an analysis of eight severe cases. *Am. J. Obst. Gynec.* 43: 467. 1942.

Nutritional edema results from a protein deficit caused by a deficiency of protein in the diet or by the loss or deficient utilization of ingested protein. It is frequently associated with anemia. Contributory factors include hot weather, overwork, the excessive ingestion of salt water, and the dependent position. In pregnancy, the protein demands of the organism are increased far above normal and cannot be met by a patient suffering from a chronically lowered protein reserve. These 8 patients revealed very marked deficiencies in protein, Fe and vitamins. The treatment, which depends on the etiology, is described.—*C. P.*

BICKERS, WM.

Effect of progesterone on uterine contractions. *Am. J. Obst. Gynec.* 43: 663. 1942.

Uterine contractions before and after the subcutaneous administration of synthetic progesterone were studied by means of an intrauterine balloon connected to a mechanical ink recorder which recorded the contractions on a kymograph. Progesterone has no effect upon uterine contractions in the normal ovulatory cycle, either during the follicular or the corpus luteum phase, or upon uterine contractions in threatened abortion or in the puerperium. It has also no effect upon the high-amplitude, hypertonic contractions of primary dysmenorrhea.—*C. P.*

BURROWS, H., D. H. MACLEOD AND F. L. WARREN.

Excretion of ketosteroids in human pregnancy urine in relation to the sex of the fetus. *Nature, London* 149: 300. 1942.

Samples of pregnancy urine were obtained from 20 women and the ketosteroids were established colorimetrically. It was later determined that 14 women were bearing male fetuses and that their average ketosteroid excretion was 26.2 mg. per liter. The six women bearing female fetuses had an average ketosteroid excretion of 14.6 mg. per liter.—*C. P.*

ELTON, N. W.

Morphologic variations in adenocarcinoma of the fundus of the uterus, with reference to secretory activity and clinical interpretations. *Am. J. Clin. Path.* 12: 32. 1942.

Cyclic changes in the morphological picture of adenocarcinoma of the uterus could be demonstrated in a series of 50 patients. It was found that the cells of the tumor responded to the secretory activity of the ovaries in a way similar to normal endometrium with the exception that the evolution of the secretory stage was slower and did not completely regress in the carcinoma cells. Some cyclic changes were also demonstrated in adenocarcinoma occurring long after the menopause. The prognosis of tumors occurring before the menopause with only menorrhagia as the chief symptom was considerably better than the prognosis of the postmenopausal group, which showed a mortality of 65%—*E. von H.*

GESCHICKTER, C. F. AND ELIZABETH BYRNES.

Factors influencing the development and time of appearance of mammary cancer in the rat in response to estrogen. *Arch. Path.* 33: 334. 1942.

The authors produced mammary cancer in 202 of 555 albino rats which were treated with estrogens. Over a period of 7 years no spontaneous mammary cancer had been observed in over 5,000 animals of the inbred laboratory stock. The author could demonstrate that all estrogens regardless of the chemical composition or physiological potency would produce mammary cancer in the rat provided that the animal survived the required time. The dose necessary was found to be well beyond the physiological limit, and the treatment must be applied continuously for a period of months. Influencing factors were the dosage, the estrogenic potency, the duration of estrogenic activity, and the method of administration. Simultaneous administration of testosterone or progesterone did not prevent or delay the appearance of mammary cancer. However, estrogenic cancer was partially inhibited by anterior pituitary extract.—*E. von H.*

GILBERT, B.

Persistent lactation with a note on Chiari and Frommel's disease. *Brit. M. J.* 2: 305. 1941.

The syndrome of puerperal uteroovarian atrophy and persistent lactation is discussed and a case is presented

of a 36 year old woman who had experienced slight but continuous mammary secretion since the birth of her only child 16 years previously. The uterus is described as small but the menstrual periods were normal. In this case lactation had apparently been maintained by daily manual manipulation of the breasts.—*E. B. A.*

HAAGENSEN, C. D., AND H. T. RANDALL.

Production of mammary carcinoma in mice by estrogens. *Arch. Path.* 33: 411. 1942.

The administration of estrone benzoate to pure bred strains of mice produced an increased incidence of breast carcinoma in the male animals to a level which was somewhat higher than in the female controls. It failed to increase the frequency of breast carcinoma in female animals of high cancer strains above the natural frequency in non-treated controls. It did not produce breast carcinoma in male or female mice of the low cancer C57 strain. It did not produce any other type of extramammary malignancy in the treated animals. The authors believe that hereditary factors supersede in importance the effect of estrogen administration on the incidence of breast cancer.—*E. von H.*

HOLLANDER, L., AND H. R. VOGEL.

Testosterone propionate in treatment of male post-climacteric dermatoses. *Arch. Dermat. & Syph.* 45: 356. 1942.

In 8 cases exhibiting various types of presenile and senile dermatitis inunction treatment with testosterone propionate was attempted. In all patients prompt improvement of the dermatitis was observed although various types of local therapy had been tried without success previously. For this reason the authors recommended the additional use of hormonal treatment in all types of post-climacteric dermatoses.—*E. von H.*

KOLLER, T.

The estrogenic substance in intra-uterine death. *Helvet. med. Acta.* 8: 639. 1941.

The content of active estrogens increased up to 400% in PU if the latter was stored for weeks or even months. The urinary estrogen content of the same subject increased with the specific gravity of the urine samples. In pregnancy with severe kidney damage, diminution in urinary estrogens occurred prior to intrauterine death of the fetus. In these patients no increase in urinary estrogens was observed before or during parturition. The amount of estrogen is not believed an important factor in induction of parturition.—*E. Fischer, in Bio. Abstracts.*

KRETZSCHMAR, N. R., AND A. C. BARNES.

The extragenital effects of diethylstilbestrol. *Am. J. Obst. Gynec.* 43: 668. 1942.

In general, the effects of diethylstilbestrol on gastro-intestinal symptoms, liver functions, body weight, renal system and hematopoietic system in women duplicated those found with the natural estrogens. None of the effects could be considered as representing toxic manifestations of diethylstilbestrol.—*C. P.*

POTH, D. O., AND S. R. KALISKI.

Estrogen therapy of tinea capitis. *Arch. Dermat. & Syph.* 45: 121. 1942.

The report included the study of 30 consecutive cases which were treated for tinea capitis with estrogens. One group of patients received estrone orally in capsules of 5,000 I.U. per day with additional local treatment of daily application of 1 gm. of ointment containing 5,000 I.U. of estrone. Other patients received diethylstilbestrol in doses of 3 mg. daily in combination with an ointment containing 125,000 I.U. per ounce. A critical analysis of the results showed that only 4 patients failed to obtain a clinical cure and those were ones who discontinued treatment. It was impossible to correlate healing time either with the amount or the type of estrogen administered. The reactions observed during or after treatment consisted in slightly tender enlargement of the breast in 2 male and 2 emale patients and 2 cases of vaginal bleeding in girls aged 3 and 5 years. Both reactions subsided promptly after the drug was discontinued.—*E. von. H.*

STURGIS, S. H., AND J. V. MEIGS.

The use of estradial diproprionate in the treatment of essential dysmenorrhea. *Surg. Gynec. and Abst.;* 75: 87. 1942.

The relative value of estradiol diproprionate is compared with other estrogens in their effect on dysmenorrhea. 260 injections were given to 33 patients. 68% of the 130 menses following treatment were painless, 11% of the pain was low, and 20% no change. The advantages of estradiol were minimum of injections and no demonstrable toxic effects.—*J. P. P.*

SUTRO, C. J., AND L. POMERANTZ.

Changes in osseous tissues of young dogs after prolonged administration of estradiol benzoate. *Arch. Path.* 33: 305. 1942.

The administration of estradiol benzoate to young mongrel dogs did not produce osteosclerosis as was observed in young mice. There was, however, an inhibition of skeletal growth and disturbance of development of the penile bone. These results suggest that other factors besides inhibition of growth may be responsible for the osteosclerosis observed in certain animals after estrogen administration.—*E. von H.*

TEAGUE, R. S.

Toxicology of the synthetic estrogen diethyl-stilbestrol and certain related compounds. *J. Pharmacol and Exper. Therap.* 75: 145. 1942.

Daily doses of the various synthetic estrogens as high as 20 mg./kg./day produced no fatalities when administered to rats. All of the compounds produced slight depression of growth and vacuolization of the liver cells which was not fatty degeneration but glycogen accumulation. In addition diethylstilbestrol when given in doses up to 100 mg./kg. daily produced an increase in weight of the liver, adrenal, pituitary and uterus and a decrease in weight of the ovary, testis, seminal vesicle and prostrate. The kidney weight was constant.—*C. P.*